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CLINICAL INVESTIGATION **Head and Neck**

VOLUMETRIC CHANGE OF SELECTED ORGANS AT RISK DURING IMRT FOR OROPHARYNGEAL CANCER

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Purpose: To assess volumetric changes of selected organs at risk (OAR) during intensity-modulated radiotherapy (IMRT) for oropharyngeal carcinoma.

Materials and Methods: Twenty-six consecutive patients that were treated with definitive IMRT ± chemotherapy between November 2007 and November 2008 were selected for the present study. As part of an internal quality assurances program, a repeat kilovolt (KV) computed tomography was planned weekly during the 7-week treatment course. On each available scan, a single observer contoured the parotid submandibular, and thyroid glands (PG/SMG/TG), larynx (L), and constrictor, masticatory, and sternocleidomastoid muscles (CM/MM/SCM) as appropriate. The volume at each scan was compared with the one at planning CT in a pair-wise fashion. p values <0.05 after correction for multiple testing were considered significant.

Results: A total of 159 scans was obtained during treatment for a total of 185 scans, including the baseline imaging. All OARs showed statistically significant changes over baseline by week 5. At week 7, the PG showed the largest absolute change with an average reduction of ~10 mL followed by both the SCM and MM (~-5 mL). The largest (~-30%) relative change was observed for the salivary glands. L and CM showed a ~15% increase in volume during treatment.

Conclusion: All selected OAR undergo significant volumetric changes during a course of IMRT for oropharyngeal squamous cell carcinoma. © 2011 Elsevier Inc.

Volumetric change, Oropharyngeal cancer, IMRT.

INTRODUCTION

Fractionated radiotherapy is based on the assumption that the dose distribution obtained at planning is delivered during each treatment session. Unfortunately, both setup errors and tissue changes can modify the dose distribution on a random—occasional or repeated—systematic basis. Shifts in the location of the isodose levels become critical for techniques that are highly conformal to the target(s), such as intensity-modulated radiotherapy (IMRT), justifying the interest in image guidance and adaptive radiotherapy (1). Because of the sharp dose gradient around the targets, subtle changes in the relative position or volume of organs at risk (OAR) may alter the planned amount of volume that receives a given dose as it has been shown for the parotid glands (2–4).

The head and neck (H&N) district is particularly complex because it contains a variety of tissues in close proximity, if not embedded, within the targets and thus exposed to significant doses of radiation. Moreover, the dose reduction to specified structures during IMRT planning may lead to an increased beam path dose to nontarget structures that may reach a level of clinical relevance (5). The patient with H&N cancer treated with (chemo)radiotherapy is also at particular risk for significant quantitative and qualitative changes in body mass composition during the course of treatment that are only partially counteracted by adequate nutritional support (6, 7).

Therefore, it is not surprising that some studies have documented parotid gland shrinkage in most patients undergoing radiotherapy for H&N cancer (2–4, 8, 9). However, based on the considerations discussed previously, we suspect that many other soft-tissue OAR may change in volume as well.

As part of a larger H&N cancer project aimed at quantifying both volumetric and dosimetric changes in selected OAR

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during a course of IMRT and perspective treatment adaptation at our institution, we report the volumetric change of selected OAR during a course of IMRT for oropharyngeal squamous cell carcinoma.

MATERIALS AND METHODS

Patients and scans

Patients treated with definitive IMRT ± chemotherapy for oropharyngeal squamous cell carcinoma at Johns Hopkins University undergo weekly kilovolt (KV) computed tomography (CT) scans in addition to the planning CT (pl-CT) as part of an internal quality assurance program. The CT scan is tentatively acquired during each week of treatment, without a fixed time interval between consecutive scans, based on the availability of the CT simulation. On each scan, selected organs at risk were retrospectively contoured as appropriate on consecutive patients treated at Johns Hopkins University over a 1-year time frame. The purpose of the present study that was approved by the local institutional review board is to describe the volumetric change of selected OAR during treatment of patients with oropharynx cancer.

OAR and contours

A single observer (F.R.) contoured the following OAR on each scan: parotid glands (PG), submandibular glands (SMG), thyroid gland (TG), constrictor muscles (CM), sternocleidomastoid muscles (SCM), masticatory muscles (MM), and larynx (L). Contours on the initial planning scan were reviewed by another radiation oncologist (G.S.). To contour the larynx, we followed a previously reported approach that focuses on the soft tissues within the cartilaginous framework (10) after further excluding the airway. For the constrictor muscles, we followed the directions illustrated by Levendag *et al.* that essentially identifies the thin muscle layer in the posterior pharyngeal wall in front of the vertebral bodies and the prevertebral muscles (11). The superior, middle, and inferior constrictor muscles were then pooled into a single region of interest. Figure 1 illustrates an example for both L and CM on an axial slice. In the contour of the MM, we included the masseter muscle and the medial and the lateral pterygoid muscles from the mandible cranially to the level of the zygomatic arch, excluding all other structures/tissues (mandible, fat) as appropriate. The SCM has been contoured from the mastoid tip down to the clavicle. Each paired OAR was divided into ipsilateral (i) and contralateral (c) with respect to the dominant side of the cancer.

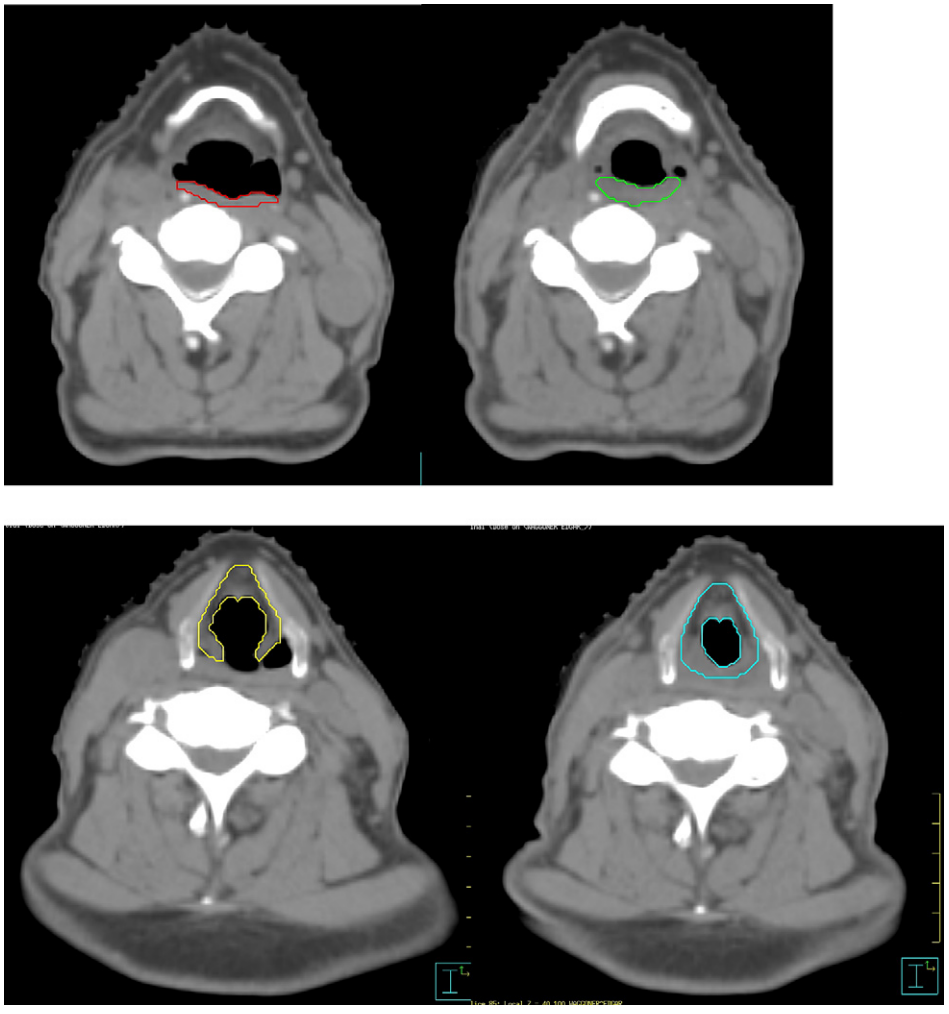

Fig. 1. Axial computed tomography (CT) scans illustrating volumetric changes of larynx and constrictors muscles. Contours at planning CT are the red and the yellow ones for constrictor muscles and larynx, respectively; the green and light blue colors represent the organs at risk at week 7.

To improve consistency of contours among scans, a propagation tool from Pinnacle[3] (Philips RadOnc Systems, Madison, WI) was used to transfer a given contour on the subsequent scan after CT-CT registration based on bony landmarks. This allowed the observer to edit the new contour based on the preceding one and to start from the same craniocaudal borders, thus minimizing uncertainties in this direction.

Contoured structures had to be clinically grossly uninvolved by the tumor and clearly identifiable on the initial pl-CT. Therefore, not all the regions of interest were contoured for each patient. Selected OAR were not available if they had been surgically removed (*i.e.*, the submandibular gland after a modified radical neck dissection) or infiltrated by the tumor to the point that the structure was no longer clearly identifiable as a separate structure on the pl-CT (*i.e.*, SCM infiltration by a neck lymph node or laryngeal infiltration by a primary tumor in the base of tongue). However, if a given OAR was available on the pl-CT, it was also contoured on all weekly CT for a given patient as appropriate.

IMRT

All patients underwent a three-level dose painting IMRT with the following total doses: 70 Gy to macroscopic disease clinical target volume (CTV1); 63 Gy to microscopic high-risk disease (CTV2); and 58.1 Gy to microscopic low-risk disease (CTV3). All doses were given for the same number ($n = 35$) of fractions over 7 weeks. In patients with upfront tonsillectomy, the dose to the tonsillar bed could have been lowered to 68.25 Gy (1.95 Gy per fraction) instead of 70 Gy, which would correspond to about 66 Gy at 2 Gy per fraction (12). Each CTV was expanded by 5 mm to the corresponding PTV.

Our IMRT approach involves a nine-field step-and-shoot technique. Dose–volume objectives are placed on both primary (brain, brainstem, cord + 4 mm) and secondary (mandible, parotids, and larynx) OAR.

Statistics

After each selected OAR was contoured on the serial CT as appropriate, its volume was extracted from Pinnacle[3]. For each observation during treatment and each OAR, we computed the absolute and the relative variation in volume compared with the one at planning. Locally weighted scatterplot smoothing curves were used to illustrate the relative change of each OAR across time.

To avoid inference by dealing with repeated data from the same patient and to investigate the effect of temporal changes on volumetric data, observed values were organized as follows. We first assigned the computed value of relative change for each OAR to a week of treatment based on the calendar day of IMRT delivery with respect to the first day of treatment (time = 0). Week 1 includes data computed from observations recorded during treatment days 1–7; week 2, days 8–15; week 3, days 16–22; and so on. For patients who had two observations during the same week of treatment, a mathematical average of the two was taken. No attempt was made to correct for missing data. Changes over baseline were compared with the Wilcoxon rank sum test in a pair-wise fashion. It should be noted that because not all contours were available for each patient, the number of pairs being compared at each time interval might vary among comparisons. Within each time frame, significance levels were adjusted with the Bonferroni-Holm correction for multiple testing (13). All tests were two-sided and statistical difference was claimed for adjusted p (a-p) values < 0.05.

Intra-observer variability was assessed for its impact on observed differences over time as follows. Within each OAR, patients were divided into three groups based on the relative change at the last available scan over baseline. From each subgroup (here defined low, intermediate, and high variation), 2 patients were randomly selected. For each of the resulting 6 patients, we further randomly selected three scans: one during the first 2.5 weeks; one during the second 2.5 weeks; and one after the fifth week of treatment. The same observer (F.R.) recontoured the repeated structures at least 2 months after the first pass using the same procedure as discussed previously and was blinded to the previous result. This resulted in 18 recontours for each OAR. The measurement error (ME) was computed as the absolute difference between the two measured volumes of the same OAR at the two readings. The percentage measurement error (%ME) that estimates intraobserver variability (14) was determined by dividing the measurement error by the average of the two measurements for each OAR. The mean, standard deviation (SD), median, and range were calculated for each OAR. Differences in measurement error between observations obtained in the various subgroups were tested with a Wilcoxon rank sum test and significance claimed for p values < 0.05.

All analyses were performed using GraphPad (version 1.03, GraphPad Software Inc., San Diego, CA) and SPSS (version 17.0, SPSS Inc., Chicago, IL).

RESULTS

Patients and treatment

The analyzed patient population consists of 26 consecutive patients treated between November 2007 and November 2008. Patient, tumor, and treatment characteristics are reported in Table 1. Median age was 54 years (range, 41–73 years). Six patients underwent upfront surgery: 2 had bilateral tonsillectomy, 2 had neck dissection, and 2 tonsillectomy and neck dissection.

Regarding nutritional status at baseline, 6 patients (23.7%) had reported dysphagia and weight loss >10%; all were started on enteral nutrition via a percutaneous endoscopic gastrostomy (PEG) tube. In the other 14 patients (53.8%), a PEG tube was inserted prophylactically before chemoradiotherapy. Pretreatment speech pathologist evaluation including swallowing assessment was performed in 14 patients (53.8%). Formal instruction on prophylactic swallowing and trismus exercises to be done twice daily throughout treatment was provided to 12 patients (46.1%). Moreover, all patients were instructed to try to continue oral intake throughout treatment despite the PEG tube.

All patients completed IMRT as prescribed except for 1 patient who missed the last fraction (total dose: 68 Gy). Median overall treatment time was 7.0 weeks (range, 6.6–9.6 weeks).

Median weight loss during treatment was -11.2% (range, +6.1% to -20.7%). Of note, 1 patient had fluid retention from chemo-related nephrotoxicity and gained weight. At a median follow-up of 13.0 months (range, 1.9–18.8 months), 5 patients remain PEG tube–dependent, 4 of these with persistent/recurrent local disease, and 1 without evidence of disease at 18.2 months from treatment completion.

Scans

Patients underwent the pretreatment pl-CT at a median time of 18 days (range, 10–27 days) before treatment start.

Table 1. Selected patient, tumor and treatment characteristics

Characteristic	Stratification	No. patients	%
Sex	Male	24	92.3
	Female	2	7.7
Primary tumor site	Tonsil	11	42.3
	Base of tongue	14	53.8
	Pharyngeal wall	1	3.8
T stage	Tx	4	15.4
	T1	5	19.2
	T2	9	34.6
	T3	4	15.4
	T4	4	15.4
N stage	Nx	4	15.4
	N0	5	19.2
	N2a	2	7.7
	N2b	5	19.2
	N2c	6	23.1
	N3	4	15.4
HPV	Positive	18	69.2
	Negative	5	19.2
	Unknown	3	11.5
Px dose to PTV1	68.25 Gy	2	7.7
	70 Gy	24	92.3
Chemotherapy	Conc platin-based	20	76.9
	Cetuximab	1	3.8
	Induction + conc	3	11.5
	None	2	7.7

Abbreviations: HPV = human papillomavirus; Px = prescribed; PTV = planning target volume; conc = concomitant.

In addition, 159 CT scans were acquired during treatment for a total number of 185 scans. Overall, we analyzed a median number of seven scans per patient (range, 5–9 scans). Table 2 reports details on the availability of each OAR by patient along with dosimetric and volumetric data at planning.

Intra-observer variability

The percentage measurement error for each OAR is summarized in Table 3. Overall, the mean and median %ME was 1.6% and 1.3%, respectively. Although the average %ME was not statistically different across all OAR, organs such as SMG and L showed the largest variation as illustrated in Fig. 2. Moreover, both variability and timing of scans did not affect %ME. Mean (SD) %ME was 1.7% (1.7%), 1.8% (1.9%), and 1.4 (1.1%) for volumes deemed to be at low, mid. and high variability, respectively (low vs. mid, $p = 0.96$; mid vs. high, $p = 0.63$; low vs. high, $p = 0.55$). Similarly, for scans takens early, at mid treatment and toward the end of treatment, the mean (SD) %ME was 1.5% (1.5%), 1.6% (1.7%), and 1.7% (1.5%), respectively (early vs. mid, $p = 0.44$; mid vs. late, $p = 0.73$; early vs. late, $p = 0.22$).

Volumetric changes over baseline

The absolute and relative mean (SD) volume changes by OAR between the pl-CT and the first and seventh week of treatment are summarized in Table 4. At week 7, as illustrated in Fig. 3, the parotid glands showed the largest average absolute volume change with a shrinkage of ~10 mL; next, both the masticator and the sternocleidomastoid muscles shrank by an average of ~4–5 mL and even smaller reductions involved both the submandibular and the thyroid glands. By contrast, the constrictor muscles and the larynx significantly increased in volume during IMRT. An example is illustrated in Fig. 1. The larynx increased in volume in all applicable patients, whereas the constrictors enlarged in 22/24 (91.6%) patients.

When volumetric changes are plotted as relative ones compared with the planning volume across time (Fig. 4), OAR can be pooled into three groups: those showing an ~30% reduction toward the end of treatment (PG and SMG); those showing smaller (5–10%) shrinkage (TG, MM, and SCM); those increasing up to an average ~15–20% during treatment (L and CM).

Regarding the timing of modifications, all structures showed statistically significant volumetric changes over baseline from the fifth week on. For the L, TG, both parotid glands, and the iSMG, a statistically significant difference

Table 2. Availability of contours for each selected structure

OAR	Patients without contours (no. of patients as per Table 2)	No. of patients with contours (no.)	Mean (SD) D at planning (Gy)	Mean (SD) volume at planning (mL)
cMM		26	40.8 (5.2)	53.6 (9.3)
iMM		26	51.1 (8.3)	54.7 (10.0)
cSCM		26	60.6 (3.0)	52.1 (13.6)
iSCM	1–3, 6, 8^, 9, 10, 19–21, 24	15	62.4 (3.0)	51.5 (13.6)
cPG		26	33.2 (2.6)†	35.3 (11.1)
iPG	2, 10, 20*	23	39.6 (7.2)	34.8 (10.2)
cSMG		26	62.2 (4.9)	9.8 (2.3)
iSMG	1*, 3*	24	69.6 (2.2)	9.5 (3.0)
TG		26	60.7 (2.6)	15.1 (6.3)
CM	20, 22	24	61.7 (4.3)	16.7 (4.3)
L	13, 20, 26	23	51.2 (7.5)‡	15.9 (3.6)

Abbreviations: OAR = organs at risk; PG = parotid gland; SMG = submandibular gland; CM = constrictor muscles; MM = masticatory muscles; SCM = sternocleidomastoid muscle; L = larynx; TG = thyroid gland; i = ipsilateral; c = contralateral; D = total dose; SD = standard deviation.

* Because of surgery; otherwise from tumor infiltration.

† 18/26 patients V30 <50%; maximum value for V30: 53.8%.

‡ 3/23 patients V50 <27%.

Table 3. Percent measurement error by OAR

	%ME				
OAR	Mean	SD	Median	Minimum	Maximum
cMM	1.3%	0.9%	1.4%	0.1%	2.8%
iMM	1.8%	1.3%	1.3%	0.2%	4.1%
cSCM	1.1%	0.7%	1.1%	0.2%	2.8%
iSCM	1.2%	0.8%	1.0%	0.2%	3.6%
cPG	0.9%	0.4%	0.9%	0.0%	1.8%
iPG	1.5%	1.1%	1.1%	0.4%	4.8%
cSMG	2.2%	2.3%	1.3%	0.0%	7.5%
iSMG	2.8%	2.8%	1.6%	0.1%	10.3%
TG	1.8%	1.2%	1.5%	0.4%	4.6%
CM	1.4%	1.0%	1.2%	0.1%	3.4%
L	2.1%	2.2%	1.4%	0.0%	8.9%

Abbreviations: See Table 2.

was already apparent from the first week of treatment (Table 4). The CM showed a significant change from the third week (mean/SD: 8.3%/12.2%, a-p = 0.04), whereas the iSCM only from the fifth week of treatment. The latter finding likely reflects the limited number of observations available for this structure because its relative change parallels that of the contralateral structure.

The masticator muscles on both sides showed an average slight increase in volume over baseline at week 1 (Table 4) and held their volume until week 4. Interestingly, at week 3, the average relative reduction was only -2.0% (SD, 5.4%; a-p = 0.14) and -1.5% (4.2%, a-p = 0.28) for the cMM and iMM, respectively, as compared with -4.5% (6.2%, a-p = 0.012) for the cSCM (with the same number of observations as MM). However, as illustrated in Fig. 4, the relative change of SCM and MM tended to converge with elapsed time.

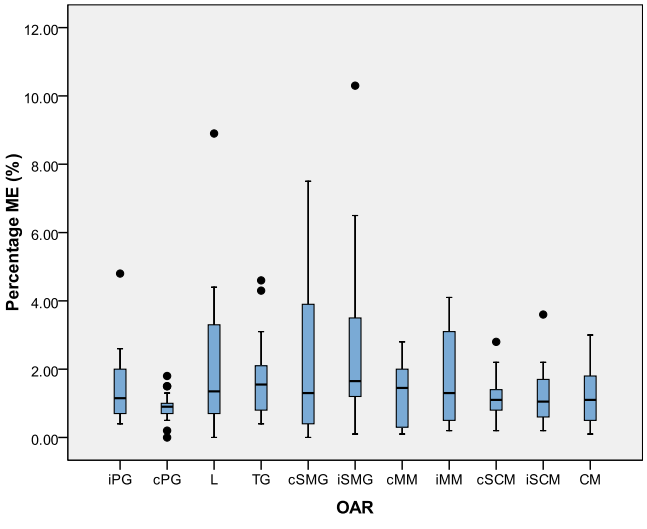

Fig. 2. Box plot of the percentage measurement error by organs at risk (OAR). *Abbreviations:* OAR = organs at risk; PG = parotid gland; SMG = submandibular gland; CM = constrictor muscles; MM = masticatory muscles; SCM = sternocleidomastoid muscle; L = larynx; TG = thyroid gland; i = ipsilateral; c = contralateral; ME = measurement error.

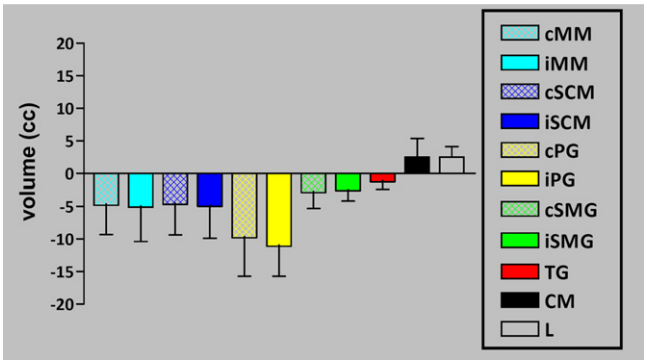

Fig. 3. Absolute volume reduction from planning computed tomography to week 7 by organs at risk. *Abbreviations:* OAR = organs at risk; PG = parotid gland; SMG = submandibular gland; CM = constrictor muscles; MM = masticatory muscles; SCM = sternocleidomastoid muscle; L = larynx; TG = thyroid gland; i = ipsilateral; c = contralateral.

All observed changes were progressive and irreversible. Once a statistically significant change over baseline was recorded for a given OAR, it was maintained or strengthened in the subsequent weeks.

DISCUSSION

In this article, we document significant modifications in volume for all selected organs at risk by the fifth week of IMRT for oropharyngeal squamous cell carcinoma. On average, the parotid glands showed the largest absolute change among the OAR considered; PG and SMG tend to show a similar relative reduction during treatment that, on average, is greater than the one of muscular structures. Both the constrictor muscles and the larynx progressively increased in volume during treatment consistent with the development of inflammation and edema.

Before commenting on these findings, we would like to clarify some methodological aspects of the present study. Serial CTs were acquired as part of an in-house quality assurance program. Therefore, CT acquisition during the course of IMRT was not at regular time intervals and the value observed during a given week was considered representative of the whole week. Moreover, not all patients had observations during each week of treatment and not all OAR were available for each patient. The baseline/pl-CT was taken several days before the actual treatment start (median, 18 days; range, 10–27) and therefore we cannot exclude that changes observed early during treatment reflect modifications that may have occurred before treatment start.

The present data illustrate the volumetric changes of selected OAR during IMRT regardless of whether radiotherapy is the sole cause or not. In this preliminary phase, we believe it is important to document the changes that occur and to what extent. Looking at the individual variation among patients (SD in Table 4), there is little doubt that the extent of changes varies considerably among patients. Despite our relatively large sample size, both missing data and correction for

Table 4. Mean (SD) absolute and relative change of each structure over baseline at weeks 1 and 7

	Week 1				Week 7			
		Mean (SD) volume change				Mean (SD) volume change		
OAR	No. patients	mL	%	a-p	No. patients	mL	%	a-p
cMM	16	0.2 (1.8)	0.5 (3.5)	0.776	22	–4.8 (4.5)	–8.2 (7.3)	<0.001
iMM	16	0.5 (1.3)	1.1 (2.9)	0.727	22	–3.6 (4.4)	–5.9 (7.3)	0.009
cSCM	16	–1.3 (2.0)	–2.3 (3.3)	0.054	22	–4.7 (4.7)	–7.8 (8.9)	0.004
iSCM	10	–1.3 (1.8)	–1.8 (4.5)	0.418	12	–5.0 (4.9)	–8.4 (10.3)	0.023
cPG	16	–2.2 (2.1)	–6.6 (5.3)	0.009	22	–9.8 (5.9)	–26.4 (11.9)	<0.001
iPG	14	–1.9 (1.6)	–5.6 (4.4)	0.019	19	–11.1 (4.6)	–31.9 (8.2)	<0.001
cSMG	16	–0.5 (0.6)	–4.6 (6.5)	0.107	22	–2.9 (2.4)	–27.3 (19.7)	<0.001
iSMG	15	–0.5 (0.5)	–4.6 (5.0)	0.026	20	–2.6 (1.6)	–26.9 (13.7)	<0.001
TG	16	–0.4 (0.4)	–3.3 (3.1)	0.036	22	–1.3 (1.1)	–8.7 (6.9)	<0.001
CM	15	0.7 (0.9)	4.8 (6.3)	0.066	21	2.5 (2.9)	16.9 (18.9)	<0.001
L	13	0.9 (0.8)	5.2 (5.2)	0.033	19	2.5 (1.6)	15.7 (9.8)	<0.001

Abbreviations: See Table 2; a-p = adjusted p value.

multiple comparisons limited the power of the analysis such that we decided not to investigate predictive factors or not to run head-to-head comparisons between OAR, reserving these for a future analysis on an expanded group of patients.

The present analysis focuses on a relatively homogeneous group of patients and tumors. Moreover, contours were drawn by a single observer with the help of a propagation tool between subsequent high-quality KVCT scans resulting in a very low measurement error. The median %ME of 1.3% of the present study compares favorably to the values of 12% and 7% reported for the primary tumor and the nodal disease, respectively (14). With the exception of iSCM, all OAR were available in at least 23 patients. Regarding the number of observations, the fact that we were able to determine changes in 142 of 182 weekly sessions (78%) is remarkable and allowed us to avoid correction for missing data. We illustrate temporal changes using as a control the locally weighted scatterplot smoothing curve that fits the framework of least squares regression but with a complex deterministic structure. Figure 4 shows good visual agreement between the locally weighted scatterplot smoothing curves computed on all observations at their original date and the computed averaged values after pooling observations by week.

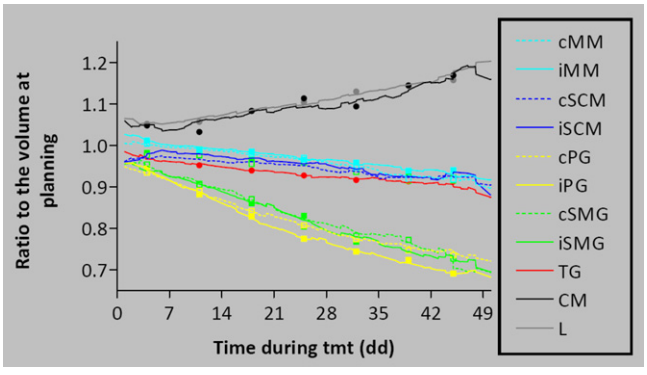

Fig. 4. Temporal relative change of volumes during treatment by organs at risk by locally weighted scatterplot smoothing curves. Dots represent the averaged observations computed for each week. *Abbreviations:* OAR = organs at risk; PG = parotid gland; SMG = submandibular gland; CM = constrictor muscles; MM = masticatory muscles; SCM = sternocleidomastoid muscle; L = larynx; TG = thyroid gland; i = ipsilateral; c = contralateral; tmt = treatment; dd = days.

Our results indicate that the parotids undergo the largest absolute and relative shrinkage during a course of fractionated IMRT. Coupled with the fact that changes are progressive and irreversible (thus representing systematic deviations) and that PG are constrained to minimize their radiation exposure at planning (and thus are adjacent to a dose gradient), the parotids represent the OAR that should be actively monitored during treatment because their anatomical changes are associated with an increase in both the daily and the cumulative doses (3). The observed average relative reduction at the seventh week (~30%) is in good agreement with the results of University of Texas MD Anderson Cancer Center (2), but it seems higher than reported by others (9, 15, 16), probably reflecting differences in several other aspects of the studies, such as the quality of the scan (MVCT vs. KVCT), the timing of the final scan, patient weight loss, the prevalence of chemotherapy, and the planned dose of radiation.

Despite earlier data suggesting that PG shrinkage correlates with the planned dose of radiation and that, especially in the setting of unilateral treatment, negligible changes occur on the contralateral or ''spared'' side (16), we show this is not the case within the range of the mean doses and volumes planned here. As shown in Table 2, on average the mean dose was ~6.5 Gy higher on the ipsilateral side ($p < 0.01$) and all cPG would have been considered ''spared'' by protocol Radiation Therapy Oncology Group 0022 (17) with (8/26, 30.8%) or without (18/26, 69.2%) minor violations. Despite these differences, significant changes were observed on both sides, as illustrated in Fig. 3 and 4. Another interesting finding is that significant anatomical changes were detected as early as the first week of treatment, though it may take several weeks of treatment to detect their effect on the cumulative dose (3). Taken together, the present data would

support checking the PG volume on both sides early during treatment (at week 2) especially if the planning CT was acquired 2–3 weeks before treatment start.

Besides adaptive implications, the present data provide insights on the pathophysiology of the damage induced by RT. The swelling of both the CM and the L a few months after the end of RT has been documented (18–20). Investigators at the University of Michigan showed an increase in thickness of the retropharyngeal space by CT 3 months after chemoradiotherapy (18). In a recent study based on repeated magnetic resonance imaging at the same time interval, they reported signal changes consistent with inflammation and edema and to a less extent fibrosis of the CM, likely as a consequence of acute mucositis affecting the submucosa-lying CM (19). Regarding the soft tissues within the larynx, Sanguineti *et al*. reported an incidence of Grade 2+ edema of 58.3 ± 7% at a median time of 17.1 months after treatment completion (10). Interestingly, here we provide evidence that changes in both CM and L parallel each other and are detectable early during IMRT suggesting a similar etiology/physiopathology and validating the hypothesis that they actually represent ''consequential'' late reactions (21). As such, this would fit the radiobiological behavior of acute reactions (22) and changes could potentially be monitored during treatment in order to minimize their late effects. That we observed changes over baseline in both CM and L in 91.6% and 100% of patients, respectively, probably reflects the higher mean doses planned in our study. A cutoff value of a mean dose of 60 Gy has been suggested for magnetic resonance imaging–based changes of CM at 3 months (19); because of the location of the primary tumor in the oropharynx and the lack of attempt to spare the CM at planning, the mean ± SD dose to CM in our experience was 61.7 ± 4.3 Gy and higher than the one reported in the previous study from the University of Michigan (52 ± 18 Gy). Moreover, we were able to achieve dosimetric laryngeal sparing only in a minority of patients (13%), likely from the use of whole-field IMRT as opposed to split-field IMRT (23). It should also be noted that none of the patients developed symptoms related to airway obstruction, though the dose to the larynx has been associated with swallowing dysfunction after treatment (24–26). For both CM and L, it will be interesting to investigate in a larger, prospective patient cohort whether dosimetric sparing translates to a better functional (swallowing) outcome.

A third implication of the present data relates to muscular changes during IMRT and the preventive role of continuous exercise and physical therapy. Silver *et al*. have documented that, despite adequate nutritional status at baseline and nutritional supplement during combined chemoradiotherapy for Stages III and IV H&N cancer, all patients started to lose weight within 1 week of treatment start and continued up to 1 month after treatment completion. Over this time, patients lost an average of 5.6 kg in lean mass, or ~10% of lean mass at baseline (6). The loss of muscle mass during treatment seems somewhat unrelated to caloric intake, but driven by the aberrant metabolic and inflammatory state of H&N cancer patients. Our results at the end of treatment for both SMC and MM are consistent with these findings (Table 2). That MM held their volume longer than SCM is unclear but intriguing. As a possible explanation, we suspect that implementation of prophylactic swallowing and trismus prevention exercises (27) along with the use of PEG tube during treatment as a backup option as opposed to a primary route of feeding may have contributed to maintaining the tone of MM. This finding is certainly important and deserves further investigation.

In conclusion, we have shown that all selected OAR undergo significant volumetric changes during IMRT. For the parotid glands, the magnitude of change may have implications for the daily dose distribution and we have shown that the parotids should be monitored for volumetric changes as early as the second week of treatment. For the remaining organs, we have shown modifications that probably have limited impact on the dose distribution but help to understand the mechanism of subacute/late injury (CM and L) and support prophylactic interventions (MM). Because we observed a high variation among patients, future studies should be directed toward the identification of factors that predict for such changes.

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