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FULL PAPER

Pattern and predictors of volumetric change of parotid glands during intensity modulated radiotherapy

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Objective: To describe the pattern and predictors of volumetric change of parotid glands during intensity modulated radiotherapy (IMRT) for oropharyngeal cancer.

Methods: A cohort of patients undergoing weekly CT scans during dose-painted IMRT was considered. The parotid glands were contoured at the time of treatment planning (baseline) and on all subsequent scans. For a given patient, the parotid glands were labelled as higher (H) and lower (L), based on the mean dose at planning. The volume of each gland was determined for each scan and the percent change from baseline computed. Data were fit to both linear and quadratic functions. The role of selected covariates was assessed with both logistic regression and pair-wise comparison between the sides. The analyses were performed considering the whole treatment duration or each separate half.

Results: 85 patients, 170 glands and 565 scans were analysed. For all parotids except one, the quadratic function provided a better fit than the linear one. Moreover, according to both the logistic regression and pair-wise comparison, the cumulative mean dose of radiation is independently correlated with the parotid shrinkage during the first but not the second half of the treatment. Conversely, age and weight loss are predictors of relative parotid shrinkage during the entire course of the treatment.

Conclusion: Parotid gland shrinkage during IMRT is not linear. Age, weight loss and radiation dose independently predict parotid shrinkage during a course of IMRT.

Advances in knowledge: The present study adds to the pathophysiology of parotid shrinkage during radiotherapy.

Fractionated radiotherapy is based on the assumption that the dose distribution obtained at planning is delivered during each treatment session. However, both set-up errors and tissue deformation can modify the dose that is administered. Shifts in the location of isodose levels compared with planning become critical for techniques that are highly conformal to the target(s), such as IMRT, justifying the interest in image guidance and adaptive radiotherapy [1]. Because of the sharp dose gradient around the target(s), subtle changes in the relative position or in the volume of organs at risk may alter the planned dose that the volume of an organ receives, as has been shown for the parotid glands [2–6].

In a study by Ricchetti et al [7], we found that the parotid glands are the regions of interest that undergo the largest absolute and relative changes in volume during treatments. Although at least 16 articles have documented a significant percent reduction in the volume of the parotid gland during the course of fractionated radiotherapy [2,3,7–20], there are still several unanswered questions. It is unclear why some parotid glands shrink to about 50–60% during treatment, while others show only minimal changes. Studies that have

investigated predictors of shrinkage have suggested weight loss during treatment, patient age and dose of radiation to the parotid as potential factors [2,9,16–19]. However, results are inconsistent [3,8,10,14]. Some studies have suggested that dosimetrically spared parotid glands undergo only minimal volume changes during treatment [16,18], whereas others describe a similar behaviour regardless of the radiation dose [7,8,10]. Furthermore, it is unclear whether the daily percent volume change is constant [8,10,16,19] or variable [7,10,13] during the course of treatment. A variable daily percent change in the volume may indicate that there are predictive factors specific to certain portions of the fractionated radiation schedule. In the present article, we attempt to clarify these points.

MATERIALS AND METHODS

Patients and scans

As previously reported, patients treated with definitive IMRT with or without chemotherapy for oropharyngeal squamous cell carcinoma at our institution underwent weekly kilovoltage cone beam CT scans, in addition to the planning CT, as part of an internal quality assurance programme. The

CT scans were tentatively obtained during each week of treatment, without a fixed time interval between the consecutive scans, based on the availability of CT simulation. In the present study, which was approved by the local institutional review board, parotid glands were contoured on each of the weekly CT scans, retrospectively, for the 85 patients treated at Johns Hopkins University, Baltimore, MD, from November 2007 to June 2010. Three observers were involved in organ contouring: FR contoured 57 pairs (67%) of parotids; a second observer, 14 pairs (16.5%) and GS, 14 pairs (16.5%). Parotid glands with gross tumour involvement had been excluded.

Intensity modulated radiotherapy

All patients underwent three levels of IMRT-based dose painting with 70 Gy prescribed to macroscopic disease (CTV1), 63 Gy to microscopic high-risk disease (CTV2) and 58.1 Gy to microscopic low-risk disease (CTV3). All doses were given in 35 fractions during 7 weeks. Each clinical target volume was expanded by 5 mm to the corresponding planning target volume. IMRT was administered with a 9-field step and shoot technique. Dose volume objectives were determined for both primary (brain, brain stem, spinal cord + 4 mm) and secondary (mandible, parotids and larynx) organs at risk. For the parotids, the dose volume objective was set at $V_{30} < 50\%$ (V_{30} being the volume that receives 30 Gy).

Statistics

The purpose of the present study is two-fold: (1) to describe the pattern of parotid shrinkage during the course of treatment and (2) to investigate the role of age, mean dose and weight loss on relative parotid shrinkage at different time points during the treatment.

For each parotid gland, the change in volume that is relative to the planning volume was calculated at each observation. In each patient, the gland that was planned to receive the higher mean dose was designated H, whereas the side to receive the lower dose was designated L.

We fit the volumetric data of each parotid gland to both linear ($y = a + bx$) and quadratic ($y = a + bx + cx^2$) equations. For each fit, r^2 that quantifies the goodness of fit was computed from the sum of the squares of the distances of the points from the best-fit curve determined using regression. In addition, we visually compared the results of the linear and quadratic fits and a locally weighted scatter-plot smoothing (LOWESS) curve to the bundled volumetric data.

To assess the role of mean dose at planning to the volumetric change during treatment, we compared, in a pair-wise fashion, the relative shrinkage of the parotid glands when receiving high dose (H) with that during low dose (L), using a nonparametric test (Wilcoxon signed-rank test).

Moreover, a multivariate logistic regression was performed on the relative parotid shrinkage data. The treatment course was divided into halves, and we investigated the predictors of volume change at the end of each half and for the overall treatment. The end point was the relative volumetric change greater than the

median value obtained for all parotid gland shrinkage measured during the first half and second half of treatment. This binary end point was chosen to ensure that the odds ratios of the parotid gland shrinkage from the treatment halves remain comparable. We included age, relative (to time of consult) weight loss (WL%) and cumulative mean dose [2,9,16], as covariates. The latter was computed as the product of the mean dose for each fraction at planning and the number of the elapsed fractions at the time of evaluation. No attempt was made to correct for dose modifications because of parotid deformation or set-up errors during the course of treatment [4,21]. All covariates were entered as continuum variables in the model. A receiver operating characteristic curve was used to identify the optimal cutoff level when the median values were not considered.

All tests were two-sided and a p -value < 0.05 was considered statistically significant. All analyses were performed using GraphPad (v. 5.0; GraphPad Software Inc, La Jolla, CA) and SPSS® (v. 17.0; SPSS Inc, Chicago, IL).

RESULTS

Patient, tumour and treatment characteristics are shown in Table 1. Median age was 57 years (range: 30–81 years). 82 of the 85 patients completed IMRT as prescribed, with 3 patients missing one or two fractions (total dose: 66–68 Gy). Median overall treatment time was 7.0 weeks (range: 6.6–8.7 weeks).

The median weight change during treatment was -8.9% (range: $+5.6\%$ to -24.7%) and was the same at -4.5% (Wilcoxon signed-rank test, $p = 0.67$) during the first and the second half of the treatment.

Scans

Patients underwent the pre-treatment planning CT examination at a median time of 19 days (range: 10–25 days) before treatment initiation. 480 CT scans were obtained from a total of 565 scans during the treatment. A median of 7 scans were analysed per patient (range: 5–9 scans). The scan closest to the chronological midpoint of treatment was chosen to assign the volumetric changes of the first and second halves. The median number of days and fractions since the start of treatment until this scan were 22 days (range: 16–28 days) and 16 fractions (range: 13–21 fractions), respectively. The median number of days and fractions since the start of treatment until the final on-treatment scan were 47 days (range: 33–55 days) and 33 fractions (range: 25–35 fractions), while the median number of days and fractions between these scans were 24 days (range: 10–33 days) and 17 fractions (range: 8–22 fractions). Baseline parotid characteristics at planning are presented in Table 2.

Pattern of relative parotid change during treatment Each observation during treatment was fit to both linear and quadratic functions. For all parotids except one on the L side, the quadratic fit provided a higher value for r^2 than the linear fit. Results are summarised in Table 3 and shown in Figure 1 for each side. Of note, the quadratic fits almost overlap the LOWESS curves entirely. Based on the quadratic fit, the average daily

Table 1. Selected patient, tumour and treatment characteristics

Characteristic	Stratification	Number of patients	Percentage
Sex	Male	77	90.6
	Female	8	9.4
Primary tumour site	Tonsil	37	43.5
	Base of tongue	46	54.1
	Pharyngeal wall	2	2.4
T stage	Tx	15	17.6
	T1	22	25.9
	T2	31	36.5
	T3	7	8.2
	T4	10	11.8
N stage	Nx	1	1.2
	N0	11	12.9
	N1	10	11.8
	N2a	5	5.9
	N2b	46	54.1
	N2c	10	11.8
	N3	2	2.4
PEG	No	17	20.0
	Yes	68	80.0
Px dose to PTV1	68.25 Gy	5	5.9
	70 Gy	80	94.1
Chemotherapy	Conc. platin-based	63	74.1
	Cetuximab	5	5.9
	Induction + conc.	7	8.2
	None	10	11.8

Conc., concentration; N stages, regional lymph nodes; PEG, percutaneous endoscopic gastrostomy; platin, platinum; PTV, planning target volume; T stages, primary tumour.

percent volume change for each side decreases as the treatment progresses (from 0.98% and 0.89% at the end of Week 2 to 0.27% and 0.35% by the end of Week 6, for sides H and L, respectively).

Percent shrinkage by side

Results are presented in [Table 4](#) along with the pair-wise comparison between sides. Overall, we observed a slight but larger statistically significant average shrinkage on the side receiving the higher mean dose at planning (+3.3%, $p=0.006$).

Results were further analysed after splitting the 85 patients by the median differences in the cumulative mean dose between the sides ([Table 4](#)). We identified 42 parotid pairs in which the median difference in cumulative dose between the sides was 2.1 Gy (0.4–6.3 Gy) at the end of treatment. In this subset that was labelled “small difference,” no appreciable difference in the relative shrinkage was evident between the sides regardless of the time course considered (first half, second half or entire treatment).

Conversely, for the remaining parotid pairs [43 patients, the median difference in the mean dose between sides 13.4 Gy (range: 6.5–27.9 Gy)], the difference in shrinkage between the two sides was statistically significant when the first half of treatment or the entire treatment course was considered but became insignificant during the second half of treatment.

According to a receiver operating characteristic curve analysis, the optimal difference in the mean dose between the sides to detect a higher than median percent difference in the shrinkage between sides ($\geq 2.7\%$) at mid-treatment is 2.5 Gy, with a sensitivity and specificity of 71.4% and 53.5%, respectively (area under the curve: 0.63, 95% confidence interval: 0.51–0.75, $p=0.039$).

Predictors of shrinkage

For all parotids ($n=170$), the likelihood of relative shrinkage exceeding the median shrinkage value of 31.1% of the cohort, as measured during the entire treatment course, correlates with the

Table 2. Parotid data at planning and/or baseline

Parameter	Number	Median	Range	Spared ^a	Borderline ^a	Not spared ^a
Volume (cc)						
Overall	170	32.6	15.9–63.5			
H	85	32.6 ^b	16.0–58.0			
L	85	33.1 ^b	4.5–62.3			
Mean D (Gy)						
Overall	170	35.2	4.5–70.4			
H	85	39.9 ^c	27.4–70.4			
L	85	33.1 ^c	4.5–62.3			
V30 (%)						
Overall	170	49.5	0.0–100.0	51.2	27.6	21.2
H	85	57.5	41.5–100.0	22.4	36.5	41.2
L	85	46.8	0.0–62.2	80.0	18.8	1.2

D indicates dose; V30, volume that receives 30 Gy; H/L, the side that receives the higher or lower mean dose at planning in a given patient.

^aSpared: V30<50%; borderline: V30>50% but <60%; not spared: V30>60%.

^bH vs L: $p=0.765$.

^cH vs L: $p<0.001$.

percentage weight loss (positive correlation) and age (negative correlation) but not the cumulative dose.

For the analysis of each half of the treatment, we used a median value of 18% in relative volume change for both time points, which was calculated from pooled observations of both the first and the second half of treatment ($n=340$). Percentage weight loss and age independently correlated with the relative volumetric change during both halves of the treatment (Table 5). The odds ratio for WL% was higher during the second half of the treatment. Interestingly, the cumulative mean dose of radiation received by each parotid gland had an independent correlation with the percent change during the first but not the second half of treatment (positive correlation).

DISCUSSION

In the present article, we have shown that the average relative parotid shrinkage during treatment is not linear, but that approximately 60% of the shrinkage occurs during the first half of treatment. Moreover, according to both pair-wise comparisons and logistic regressions, the cumulative dose of radiation has

a detectable and independent effect on the parotid shrinkage only during the first half of the treatment. Therefore, a larger shrinkage is to be expected during the first half of the treatment on the side that receives the higher dose, especially when the difference in the cumulative dose with the contralateral side is >5 Gy at planning.

In many ways, these results help to interpret the data from current literature (Table 6). Consistent with our findings, articles that dealt with a younger patient population showed the highest rates of percent reduction in the parotid gland volume at the end of treatment [3,19]. Age was also an independent predictor of shrinkage in the article by Broggi et al [9].

Regarding the effect of dose on parotid shrinkage, we suspect that two issues have contributed to the frequent inability to detect a correlation: (1) the spread of mean doses to the parotids is limited, especially in the studies that included patients treated with conformal radiotherapy and (2) the effect of dose may have been masked by other covariates, especially if patients underwent significant weight loss during the course of a treatment.

Table 3. Goodness of fit (r^2) to both linear and quadratic functions of percent change of parotid gland volume by side

Side	Curve fit	Number of patients	Goodness of fit (r^2)		p -value ^a
			Mean	SD	
L	Linear	85	0.906	0.159	<0.001
	Quadratic	85	0.954	0.077	
H	Linear	85	0.900	0.138	<0.001
	Quadratic	85	0.954	0.075	

H/L indicates the side that receives the higher or lower mean dose at planning within a given patient; SD, standard deviation.

^aWilcoxon signed-rank test.

Figure 1. Percent change in parotid gland volume during the course of intensity-modulated radiotherapy by the side that receives the higher (a) or lower (b) mean dose at planning for a given patient. Blue line (black in print), linear regression fit; red line (thick grey), quadratic regression; yellow (thin grey), locally weighted scatter-plot smoothing curve; tmt, treatment.

For example, in an article from the University of Texas: MD Anderson Cancer Center, 13 of the 14 patients were treated with three-dimensional conformal radiotherapy, suggesting that the mean parotid dose, though not reported, was on average high and consistent among patients [2]. Interestingly, the authors found a close relationship between the percent weight loss and the medial shift in the parotid centre of mass (Spearman's ρ (ρ)=0.93, $p<0.001$) instead of parotid shrinkage [2]. On the contrary, Vasquez Osorio et al [16] analysed 10 oropharyngeal patients treated with IMRT only to 46 Gy and mostly without chemotherapy. The planned mean parotid doses ranged from approximately 5 Gy to 35 Gy, and a significant correlation between the planned mean doses and the volume changes was detected (ρ =0.68, $p<0.001$). In another article, Wang et al [18] analysed the parotid shrinkage in 82 patients with various head and neck primary tumours, approximately 50% of whom were treated with IMRT and the remaining with conformal three-dimensional radiotherapy. The authors describe a significant correlation between the mean dose at planning and the percent shrinkage at the end of the treatment (ρ =0.405, $p<0.001$). Similar to that found in the data of our study, further analyses of

their results show an evident effect of dose only during the first half of the treatment, whereas the percent reduction during the second half was not correlated with the delivered dose. Moreover, they found that the average volume loss rate of the parotid glands during the first 3 weeks of radiotherapy was significantly larger than during the last 3 weeks of radiotherapy (20.0% vs 8.6%, respectively, $p<0.001$).

It is unclear why only the first part of the treatment shows a correlation with the cumulative mean dose (computed as the planned dose of each fraction and the number of fractions delivered without considering both set-up errors [21] and parotid volumetric changes [4]). This may reflect a deterioration in the dose distribution during treatment to a point where the mean dose at planning is no longer representative of the actual delivered dose. However, one study that computed the delivered cumulative dose to the parotids based on daily estimations found that only 3 of the 10 patients showed significant deviations from the planned one, and this was always in-line to overdosing [4]. Few more studies on another cohort of 10–12 patients failed to provide consistent results on both the magnitude and direction of change in the mean dose of the parotid gland during a course of IMRT, although none of them showed, on average, a decrease in the dose during treatments [22–24]. Although data on more patients are required to elucidate this issue, this contrasts with the fact that we found a slower rate of shrinkage during the second half of the treatment.

Alternatively, one may hypothesise that the early reduction in parotid volume reflects the damage of the more radiosensitive acinar cells [25]. In a previous study, on a partially overlapping patient population, the parotid density (Hounsfield number on kilovoltage cone beam CT) was shown reduced in most of the patients during IMRT, and this phenomenon was highly correlated with the parotid deformation [26] that in a previous study had been found to be correlated with the parotid dose at planning [27]. Because normal parotid glands contain abundant adipose tissue [26], it is not surprising that their shrinkage parallels the treatment-related weight loss [2]. Ageing is associated with acinar atrophy and with a relative increase in both adipose and fibrovascular tissues [28]; the presence of the latter would support our observation of less shrinkage in older patients, also during the second half of treatment.

Future work will need to clarify the relationship between parotid shrinkage and decreased organ function. So far, none of the studies have shown a clear correlation between the degree of parotid shrinkage at the end of the treatment and xerostomia. In a retrospective study using CT along with [^{18}F]-fludeoxyglucose-positron emission tomography (^{18}F -FDG-PET), a sigmoid relationship was found between the average standard uptake values and the parotid mean dose; however, parotid shrinkage on CT within 3 months from treatment was uniform and unrelated to the dose [29]. Altogether, these data suggest that if a correlation between dose, shrinkage and function exists, it would be detected most likely during the early stages of treatment.

We acknowledge that this article has some limitations, with some of them having been extensively discussed before [7].

Table 4. Pair-wise comparisons of percent volume change of parotid glands during the whole treatment or each separate half

Observation time	Subset	Side	Number	Median cumulative dose (range) ^a	Percent change		<i>p</i> -value ^b
					Mean	SD	
Whole tmt	All	H	85	38.0 (22.0–64.2)	66.0	13.7	0.006
		L	85	30.8 (3.9–48.6)	69.3	12.9	
	Small diff	H	42	33.7 (22.0–53.3)	66.7	11.4	0.39
		L	42	31.3 (20.6–48.6)	69.5	11.6	
	Large diff	H	43	42.6 (28.2–64.2)	65.4	15.8	0.005
		L	43	29.9 (3.9–36.3)	70.3	13.1	
First half	All	H	85	18.4 (11.7–35.1)	77.6	11.4	0.007
		L	85	15.1 (2.4–32)	80.0	10.3	
	Small diff	H	42	16.6 (11.7–34.0)	78.3	11.1	0.41
		L	42	15.2 (11.1–32.0)	79.2	10.5	
	Large diff	H	43	21.0 (12.2–35.1)	76.9	11.8	0.005
		L	43	15.1 (2.4–20.2)	80.7	10.1	
Second half	All	H	85	19.3 (7.9–35.9)	85.2	15.0	0.701
		L	85	15.3 (1.5–22.0)	86.8	14.4	
	Small diff	H	42	17.6 (7.9–24.1)	85.1	7.8	0.817
		L	42	16.4 (7.4–22.0)	85.3	10.1	
	Large diff	H	43	21.7 (10.8–35.9)	85.4	19.8	0.798
		L	43	14.4 (1.5–20.3)	88.3	17.7	

Diff., difference; H/L, the side that receives the higher or lower mean dose at planning in a given patient; SD, standard deviation; small diff, difference in the mean dose between sides (H vs L) $\leq$ the median cutoff; tmt, treatment.

^aNot accounting for set-up errors or deformation

^bWilcoxon signed-rank test.

Results are further stratified by the difference in the mean cumulative dose at each observation: large difference, the difference in mean dose between sides (H vs L) is greater than the median cutoff.

Bold *p*-values are statistically significant (<0.05).

Table 5. Logistic regression including selected covariates considering the whole treatment and each separate half

Predictor	Covariate		
	Weight loss (%)	Cumulative mean dose (Gy)	Age (years)
Whole tmt			
OR	1.190	1.010	0.950
95% CI	1.09–1.31	0.97–1.05	0.92–0.99
<i>p</i> -value	<0.001	0.699	0.011
First half			
OR	1.160	1.080	0.960
95% CI	1.04–1.29	1.01–1.17	0.93–0.99
<i>p</i> -value	0.007	0.038	0.033
Second half			
OR	1.360	1.020	0.940
95% CI	1.18–1.58	0.94–1.10	0.90–0.98
<i>p</i> -value	<0.001	0.632	0.005

CI, confidence interval; OR, odds ratio; tmt, treatment.

Bold *p*-values are statistically significant (<0.05).

Table 6. Literature data on parotid gland shrinkage during radiation therapy

Study	Number of patients	Age (years)	Site	Tech	Mean parotid dose (Gy)	CHT	WL%	CT scan	Number of scans per patient and timing	Mean volumetric change
Han et al [3]	5	48	NPC	HT	NR	NR	-8.5%	MVCT	8 (weekly)	-40.2%
Barker et al [2]	14	55	M	93% 3DCRT	NR	92.8%	-7.1%	KVCT	18-21 (Week 3)	-1.1%/tmt d
				7% IMRT						-28.1%
Hansen et al [11]	13	54	M	IMRT	NR	100%	4-14%	KVCT	2 (Week 4)	-0.6%/tmt d
										R: -15.6%
Robar et al [15]	15	59	M	IMRT	NR	66.6%	-7.5%	KVCT	4-7	L: -21.5%
										R: -5.0% week ⁻¹
Vasquez Osorio et al [16]	10	60	Oro	IMRT	H: 25.1	10%	NR	KVCT	2 (end)	L: -4.7% week ⁻¹
					L: 7					Overall: -14%
										H: -17%
										L: -5%
Lee et al [13]	10	NR	M	HT	NR	90%	-3.3%	MVCT	33 (daily)	-21.3%
										-0.7%/tmt d
Wang et al [18]	82	52	M	51% 3DCRT	22.2/50.2 (IMRT/3DCRT)	None	NR	KVCT	3 (Week 3, end)	3 weeks: -20%
				49% IMRT						-1.4%/tmt d
										end: -26.9%
										-0.57%/tmt d
Broggi et al [9]	87	58	M	IMRT/HT	32.7	86.2%	-8%	KVCT	2 (end)	-26%
								MVCT		
Ricchetti et al [7]	26	54	Oro	IMRT	H: 39.6	88.5%	-11.2%	KVCT	4-8 (weekly)	H: -31.9%
					L: 33.2					L: -26.4%
Wu et al [19]	18	51	NPC	3DCRT	≈55-60	None	NR	KVCT	2 (end)	-35%
Castadot et al [10]	10	57	M	IMRT	H: 27.4	100%	NR	KVCT	NR (weekly)	H: -0.9%/tmt d
					L: 20.3					L: -1%/tmt d

(Continued)

Table 6. (Continued)

Study	Number of patients	Age (years)	Site	Tech	Mean parotid dose (Gy)	CHT	WL%	CT scan	Number of scans per patient and timing	Mean volumetric change
Height et al [12]	10	58	M	IMRT	NR	90%	-3%	KVCT	2 (Week 5)	H: -23.6%
Loo et al [14]	5	51	M	HT	H: 33.8 L: 26.2	100%	NR	MVCT	9 (weekly)	L: -20.5%
Wang et al [17]	15	NR	NPC	IMRT	NR	100%	-8%	KVCT	2 (Week 4)	H: -30.2%
Bhide et al [8]	20	NR	M	IMRT	H: 38.4 L: 24.3	100%	-7.5%	KVCT	5 (Weeks 2-5)	L: -17.5%
Fiorentino et al [20]	10	54	M	IMRT	H: 33 L: 31	80%	NR	KVCT	14	R: -20.6%
Present study	85	57	Oro	IMRT	H: 39.9 L: 33.1	88.2%	-10.1%	KVCT	4-8 (weekly)	L: -19.8%
										-15% by Week 2
										-31% by Week 4
										H: -43.5%
										L: -44.1%
										H: -34%
										L: -30.7%

3DCRT, conformal three-dimensional radiotherapy; CHT, chemotherapy; D, dose; H/L, the side that receives the higher (H) or lower (L) mean dose at planning in a given patient; HT, helical tomotherapy; IMRT, intensity modulated radiotherapy; KVCT, kilovoltage cone beam CT; M, multiple sites; MVCT, megavoltage cone beam CT; NPC, nasopharynx; NR, not reported; Oro, oropharynx; R/L, right/left; Tech, technique; tmt d, per day of treatment; WL%, percent weight loss.

Another aspect of our article that deserves some comments is that the mean planned dose to the parotids (Table 2) was higher than in other articles (Table 6). This is because of the fact that we used parotid V30<50% as a dose objective, and we tried to avoid underdosing the low-dose planning target volume [30]. As summarised in Table 2, all but one patient had at least one parotid gland marginally spared (V30<60%). Although we believe that this does not affect the analysis, it might be required when comparing our percent rates with those of other studies. Moreover, one may argue that because the study was not prospectively designed, the resulting halves of the treatment course are not equal in fractions, doses and days; however, pair-wise comparison of the whole group and the two subgroups

(small/large difference) failed to reveal any significant difference in any of these features (data not shown). Finally, based on the available literature, we decided to limit the analysis to three covariates [2,9,16]. However, univariate analysis of other factors, such as sex, primary tumour location, T stage and concomitant chemotherapy failed to show any significant correlation with percent change (data not shown).

In conclusion, age, weight loss and dose at planning are independent predictors of parotid shrinkage during IMRT. The observed pattern of shrinkage of both parotids during IMRT is not linear, with most of the shrinkage occurring during the first half of treatment.

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