Xerostomia, salivary characteristics and gland volumes following intensity-modulated radiotherapy for nasopharyngeal carcinoma: two year follow-up

Christina PC Sim[a,b,c]*, Yoke-Lim Soong[b,d], Eric PP Pang[d], Cindy Lim[e], Glenn D Walker[c], David J Manton[c], Eric C Reynolds[c], Joseph TS Wee[b,d]

[a]Department of Restorative Dentistry, National Dental Centre Singapore, 168938, Singapore

[b]Duke-NUS Medical School, 169857, Singapore

[c]Oral Health Cooperative Research Centre, Melbourne Dental School, University of Melbourne, Victoria 3010, Australia.

[d]Division of Radiation Oncology, National Cancer Centre Singapore, 169610, Singapore.

[e]Division of Clinical Trials & Epidemiological Sciences, National Cancer Centre Singapore, 169610, Singapore.

*Corresponding author at: Department of Restorative Dentistry, National Dental Centre Singapore, 5, Second Hospital Avenue, Singapore 168938, Singapore. Tel: + 65 63248928. Email: christina.sim.poh.choo@singhealth.com.sg

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DR. CHRISTINA PC SIM (Orcid ID : 0000-0001-8597-1786)

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ABSTRACT

Background: To evaluate changes in xerostomia status, salivary characteristics and gland volumes two years following radiotherapy in nasopharyngeal carcinoma patients. **Methods:** Xerostomia scores, salivary flow rates, pH and buffering capacity were measured at pre-radiotherapy, mid-radiotherapy, two-weeks, three-months and two-years post-radiotherapy. Salivary gland volumes and their correlation with radiation dose were also assessed. **Results:** Mean radiation dose to oral cavity, parotid and submandibular glands was 44.5, 65.0 and 38.6 Gy respectively. Parotid and submandibular gland volumes decreased 33% at three months post-radiotherapy ($p<0.001$); volumes at two years post-radiotherapy were 84% ($p=0.005$) and 51% ($p<0.001$) of pre-radiotherapy levels, respectively. Correlations were observed between parotid gland volume percent reduction and its radiation dose ($r=0.531$, $p=0.003$) and between resting salivary flow rate reduction and post-radiotherapy/pre-radiotherapy submandibular gland volume ratio ($r=-0.518$, $p=0.048$). Salivary flow rates and resting saliva pH remained significantly low at two years post-radiotherapy: both flow rates ($p=0.001$); resting saliva pH ($p=0.005$). Similarly, xerostomia scores remained significantly higher compared with pre-radiotherapy levels ($p=0.003$). **Conclusion:** Submandibular gland volumetric shrinkage persisted two years after radiotherapy. Xerostomia scores remained

significantly higher, and salivary flow rates and resting saliva pH remained significantly lower, suggesting that study participants were still at risk for hyposalivation-related oral diseases.

Keywords: Head and neck cancer; Intensity-modulated radiotherapy; Nasopharyngeal carcinoma; Salivary glands; Xerostomia

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is endemic in select geographic and ethnic populations, occurring 2-3 times more frequently in males than in females[1]. The majority of cases occur in south-east and east Asia, northern Africa and Alaska. In males, the reported age-standardised incidence of NPC in south-east Asia is 6.4 per 100,000 compared with an age-standardised incidence of 0.7 per 100,000 in Australia/New Zealand[1]. The ethnic Chinese and Inuits are predisposed to the disease[2, 3]. In Singapore, NPC is the most common head and neck cancer affecting Singaporean males; 92.5% are of Chinese ethnicity[4]. It arises from the epithelium of the nasopharynx and is commonly detected at the fossa of Rosenmüller[2]. The nasopharnyx is located below the central base of the skull making surgical access difficult. As NPC is highly radiosensitive, radiotherapy (RT) is the primary treatment modality[2]. Radiotherapy for NPC is extremely challenging due to the proximity of the post-nasal space to many critical organs, including salivary glands, optic nerve and brainstem. Radiation damage to these structures often results in long-term morbidity[5, 6]. Hyposalivation and the related xerostomia have a significant impact on the overall health-related Quality of Life[7, 8]. An important oral sequela arising from hyposalivation is the increased risk of radiation caries, characterised by rapid onset and progression and can occur at any part of the tooth surface, even those not usually susceptible to the disease[9-11]. Low salivary flow and increased acidity of the oral environment favour the overgrowth of acidogenic and aciduric oral microbiota with increased acid production, resulting in the dissolution of tooth minerals[12-14].

Currently, the standard treatment modality for NPC is intensity-modulated radiotherapy (IMRT) with or without chemotherapy[2]. Improved tumour target coverage with significant sparing of major sensitive tissue structures such as the parotid glands (PG) is possible with IMRT[15]. Despite advances in RT techniques, radiation effects on salivary glands persist, as the submandibular, sublingual and minor salivary glands are included in the treatment portal,

especially when bilateral irradiation is carried out[16] as usually performed with most NPCs. The aim of this study is to evaluate the changes in xerostomia status, salivary characteristics and gland volumes in NPC patients two years after completion of IMRT.

METHODS

Consecutive, newly diagnosed NPC patients requiring IMRT and referred by the National Cancer Centre Singapore to the National Dental Centre Singapore for pre-RT oral health clearance were recruited over a nine month period. Eligible participants completed pre-RT oral health clearance and gave written informed consent. Individuals receiving palliative care or who had previously undergone head and neck RT, were excluded. The Singhealth Centralised Institutional Review Board approved the study.

Sample size was calculated with G Power version 3.1 sample size package[17] based on a two-tailed paired t-test. Assuming a SD of 5% based on previous research with α set at 0.05 and a 35% attrition rate, a sample of 24 participants were recruited to detect a difference in mean stimulated saliva flow rate of 0.4 mL/min with a power of 90%.

Treatment planning and treatment delivery

All participants were staged using magnetic resonance imaging (MRI) post-nasal space, computed tomography (CT) chest/abdomen and bone scan, according to the American Joint Committee on Cancer (AJCC) guidelines[18].

They were immobilised in a supine position with the neck neutrally positioned with an in-house fabricated four-point thermoplastic mask (Klarity Medical & Equipment Co. Ltd, Guangzhou, China) and customised headrest (alpha cradle; Smither Medical Products Inc., OH, USA). Intravenous contrast-enhanced CT simulation was performed at 2.5 mm intervals using a GE Lightspeed 16-slice large bore CT simulator (GE Medical Systems Inc., WI, USA). Digital imaging and communications in medicine (DICOM) images were imported to the treatment planning system (Varian Eclipse™ v10.0, PA, USA), where MRI co-registration was performed. The gross target volume included all known gross disease (primary tumour plus grossly enlarged lymph nodes) as determined by the imaging, clinical, and endoscopic findings. The clinical target volume (CTV) was contoured according to the Radiation Therapy Oncology Group 0615 protocol. A 3-5 mm expansion was applied from the CTV to derive the planning target volume (PTV). Contouring of the organs-at-risk (i.e. PGs, submandibular glands (SMGs) and oral cavity) was performed by a credentialed

physician. The oral cavity was outlined as a 'distinct' organ as previously described[16]. The contoured volumes were reviewed and approved by the attending radiation oncologists.

All participants received IMRT at a prescribed dose of 70 Gy in 33 to 35 fractions to the PTV of gross tumour, delivered in 2.0 to 2.12 Gy per fraction over a period of 6.5 to 7 weeks. Areas of high risk for subclinical disease received 60 Gy. This included the entire nasopharynx, anterior 1/2 to 2/3 of the clivus (entire clivus, if involved), skull base (foramen ovale and rotundum bilaterally included for all cases), pterygoid fossae, parapharyngeal space, inferior sphenoid sinus (in T3-T4 disease, the entire sphenoid sinus) and posterior fourth to third of the nasal cavity and maxillary sinus (to ensure pterygopalatine fossae coverage) as well as retropharyngeal and level I to IV neck nodes bilaterally. The IMRT was delivered via a 9-field 6 MV co-planar sliding window using a Varian linear accelerator (Varian Medical Systems, Palo Alto, CA) or tomotherapy (TomoTherapy Inc., WI, USA) in a single volume. Treatment setup positions were verified at least twice weekly during treatment. Participants with non-metastatic stage III and IV NPC also received cisplatin 100 mg/m^2 on week one, four and seven of radiation followed by three cycles of adjuvant cisplatin 80 mg/m^2 on day one and 5-fluouracil 1 g/m^2 on days one to four.

All participants had diagnostic CT scans to assess response, performed at three months and two years post-RT. The resultant DICOM images were imported into the same treatment planning system, and the salivary glands re-contoured and volume measured. Mean doses of the contoured volumes were recorded from the dose volume histograms in the approved treatment plan. Mean PG and SMG radiation dose was derived from the average of the respective mean right and left gland doses. Total gland volumes were calculated as the sum of the respective right and left gland volumes.

Xerostomia assessment

The clinician-rated xerostomia score was determined using the Radiation Therapy Oncology Group/European Organisation for the Research and Treatment of Cancer (RTOG/EORTC) radiation morbidity scoring criteria[19] before RT (Pre-RT), at mid-RT (Mid-RT), two weeks (Post-RT-2w), three months (Post-RT-3m) and two years (Post-RT-2y) post-RT. Participants' self-assessment of xerostomia status was determined using a xerostomia-related questionnaire (XQ), consisting of eight questions evaluating chewing, swallowing, speaking and sleeping functions[16]. Participants rated each symptom on an 11-point Likert scale (0 to 10). A

summary score was derived by adding each item score; higher scores represented greater xerostomia levels.

Saliva assessment

Participants refrained from eating and drinking for 60 min before saliva collection. For resting saliva collection, participants sat in a relaxed position with the head tilted slightly forward and expectorated repeatedly into a pre-weighed container for 10 min. Resting saliva volume was measured gravimetrically, assuming a specific gravity of 1.0 and the flow rate (mL/min) recorded[20]. For stimulated saliva collection, participants chewed for 10 mins on a piece of non-flavoured wax, expectorating regularly into a pre-weighed container. Saliva pH was determined using a pH meter (Orion 9810BN, Thermo Scientific, MA, USA), within an hour after saliva collection. Stimulated saliva buffering capacity was determined according to manufacturer's instructions (Saliva-Check Buffer®, GC Corp., Tokyo, Japan).

Statistical analysis

Means of salivary flow rates, pH, buffering capacity and XQ score were compared across the five study visits using a linear mixed model with time as the fixed (repeated within-patient) factor and patient as the random factor[21]. Post-hoc comparisons of differences across study visits were performed on the marginal means using the Sidak adjustment for multiple comparisons. Salivary gland volumes measured at post-RT-3m and post-RT-2y were compared to pre-RT values using the paired t-test. Correlations between salivary gland volume percent reduction and radiation dose; and between salivary flow rate reduction and post-RT/pre-RT gland volume ratio were measured using Spearman's Rank Correlation Coefficient. P-values < 0.05 indicated statistical significance. Statistical analyses were performed using SPSS version 22 (IBM SPSS Statistics for Windows, NY, USA).

RESULTS

The demographic and clinical characteristics of the 24 newly diagnosed NPC patients recruited are described in Table 1. During RT treatment, one had dysphagia due to severe mucositis, three had nasogastric feeding tubes and two had neutropenia and were hospitalised. All participants completed IMRT as prescribed. Two participants dropped out at mid-RT as they were too ill to continue with the study. Fifteen completed the two year follow-up (four were uncontactable and three refused to return).

The radiation dose delivered to the salivary glands and the oral cavity is described in Table 2. Both PGs and SMGs showed similar volumetric shrinkage of 33% at post-RT-3m ($p < 0.001$) (Fig. 1). At post-RT-2y, whilst the PGs recovered to around 84% of pre-RT levels ($p = 0.005$), the SMGs continued to shrink to 51% of pre-RT volumes ($p < 0.001$)**.** At post-RT-2y, a moderate but statistically significant correlation between PG volume percent reduction and PG mean radiation dose was observed ($r = 0.531$, $p = 0.003$).

The incidence of participants experiencing RTOG/EORTC Grade 0, 1, 2, 3 and 4 xerostomia score is summarised in Table 3. The mean XQ score increased during RT and peaked at mid-RT. At post-RT-2y, it remained significantly higher compared with pre-RT levels ($p = 0.003$).

All salivary parameters decreased significantly at post-RT-3m ($p < 0.001$ for all) (Table 4). By post-RT-2y, resting and stimulated salivary flow rates remained significantly below pre-RT levels ($p = 0.001$ for both). Stimulated salivary pH and buffering capacity recovered to pre-RT levels by post-RT-2y; resting salivary pH however, remained significantly lower ($p = 0.005$). A moderate statistically significant inverse correlation between reduction in resting salivary flow rate and post-RT/pre-RT SMG volume ratio ($r = -0.518$, $p = 0.048$) was observed at post-RT-2y.

DISCUSSION

The present study showed that the effects on xerostomia status, salivary characteristics and gland volumes were significant and remained so two years after completion of IMRT. At post-RT-3m, both PGs and SMGs showed significant volumetric reduction of 33%. By post-RT-2y, the PGs showed partial volumetric recovery but still remained significantly smaller relative to pre-RT volumes. The SMGs however, continued to shrink and by post-RT-2y, were reduced to half their original volume. This could be partially attributed to the high radiation dose received by the SMGs as the reported cumulative dose threshold values for the potential recovery of SMG function over time was $\leq$ 39 Gy[22], a much lower level than observed in the present study.

Following RT, participants experienced significant declines in all salivary parameters measured, which would have resulted in disruption of homeostasis of the oral environment. Homeostasis of the oral environment was not fully restored at post-RT-2-y, as reflected by the significantly low salivary flow rates and resting pH; conditions associated with high

caries incidence and susceptibility[23, 24]. Restoration of oral homeostasis would likely not be possible as the stimulated salivary flow rate was < 1.0 mL/min; the proposed threshold value for the recovery of oral bacterial species associated with homeostasis [13]. Study participants therefore remained at increased risk for caries[12, 14]. Management of radiation caries would thus benefit from the life-long daily use of topical neutral fluoride gel supplemented with calcium-containing remineralising agents[10, 25, 26]. However, long-term compliance to fluoride use is unreliable[27, 28], highlighting the importance of regular assessment of oral health to detect and manage early signs of caries risk.

Despite the use of IMRT, participants experienced significant increase in xerostomia levels as early as week 4 of RT; and which remained significantly high at post-RT-2y. The slight improvement in XQ scores at post-RT-2y could partly be attributed to the partial recovery in salivary flow rates. As the SMG received 65 Gy and continued to show volumetric shrinkage at post-RT-2y, in contrast to the observed partial volumetric recovery of the PG, improvement in XQ scores and salivary flow rates probably arose from an improvement of PG function.

Saliva secreted from the submandibular and minor salivary glands contains mainly mucins, and its sero-mucous consistency has a better lubricating effect on oral soft tissues than the serous parotid gland secretions[29]. This is of major clinical significance as it influences the xerostomia experience of the patients. In health, about 65% and 10% of the resting salivary flow is contributed by the submandibular and minor salivary glands, respectively[30]. At a high dose of 65 Gy, SMG output would be severely compromised or negligible; as such, improvement in resting salivary flow over time may be due to the relatively greater contribution from the PG. However, the lack of mucinous saliva and altered mucin glycosylation[31] would result in inadequate lubrication of the soft tissues. Thus, in patients with high radiation dose to the SMGs, their perception of dry mouth may not be completely resolved despite improvement in PG function over time.

A proposed advantage of IMRT is that it provides for improved tumor targeting with sparing of major sensitive tissues such as the PGs, if they are not affected by the tumour. This approach allowed for the possibility of reducing the prevalence and severity of salivary gland hypofunction, thus increasing the likelihood for the recovery of post-RT salivary flow over time[15, 16]. A variety of mean cumulative dose threshold values for the PGs above which gland damage was irreversible has been reported; these ranged from 26 to 40 Gy[8]. The wide range

in reported dose threshold values reflected the varied mix of different head and neck cancer diagnoses included in the different studies, rendering interpretation and comparison of data across studies difficult. Total dose to both PGs and SMGs may also be a predictor for Grade ≥ 3 xerostomia for various types of head and neck cancers except for NPC[32]. Another possible predictor for xerostomia is the radiation dose to the oral cavity, which represents the minor salivary glands[16]. In the present study with a small sample size, instead of all head and neck cancer patients, only NPC patients treated with IMRT were included due to limited resources. This reduced the effects of disease and radiation protocol variability minimizing variation in baseline variables. The study results however, might not be generalisable to all head and neck cancers.

The significant inverse correlation between the reduction in resting salivary flow rate and post-RT/pre-RT SMG volume ratio observed in the present study highlights the importance of preserving SMG volume. This study appears to be the first to show the long-term effects of IMRT on SMG volume and its relation to salivary flow rates in NPC patients. The SMGs are smaller than the PGs, but they received the highest mean radiation dose, resulting in a lower recovery of the resting salivary flow rate at two years post-RT, relative to the stimulated salivary flow rate. This is also partly attributed to the lack of dose constraints on the SMGs with optimisation priority directed to spare the PGs when possible. A SMG mean dose of < 50 Gy and an oral cavity mean dose of < 40 Gy are associated with low patient-reported and observer-rated xerostomia[33]. Techniques to reduce the radiation dose to SMGs include sparing of the contralateral SMG[34] and SMG translocation for patients for whom surgery is the primary mode of treatment[35]. In NPC involving bilateral lymph nodes, sparing the SMGs or PGs may be problematic as the level Ib and II lymph nodes are in close proximity to these glands. In the present study, all participants except two had lymph node involvement, reflected in the higher radiation doses received by the oral cavity and the SMGs compared with the PGs.

Planning objectives are primarily given to spare the critical structures such as the spinal cord, brainstem and optic chiasm before optimising doses to the target volume. Although level Ib lymph nodes are traditionally considered at risk and treated for all cases of NPC, several studies have shown that the incidence of level Ib lymph node involvement at presentation ranges from 0.3% to 2.7%[36, 37]. Furthermore, it may be possible to predict patients at higher risk of level 1b involvement, such as those presenting with oropharyngeal involvement,

maximal diameter of level IIa lymph nodes > 2 cm, level IIa nodes with extra-capsular spread and positive bilateral cervical lymph nodes[37, 38]. This led to the proposal that level Ib sparing with IMRT may be safe and feasible for selected patients. Level Ib lymph nodes should still be treated if involvement by NPC extends to areas that drain to level Ib nodes, such as the medial canthus, lower nasal cavity, oral cavity including the hard and soft palate, lips, and the anterior tongue[39].

The use of salivary substitutes and pilocarpine, a cholinergic stimulant, to provide symptomatic relief for patients suffering from hyposalivation has been extensively studied, with mixed results[40]. In recent years, several innovative strategies such as salivary stem cell transplantation and tissue bioengineering approaches have been explored with the aim to regenerate and restore salivary gland function, but these novel solutions have yet to be translated to clinical practice[41, 42]. Due to its unique energy absorption profile, proton therapy has a distinct advantage compared with x-ray (photons) therapy in optimising radiation dose to the target region without increasing dose and the resultant toxicity to the surrounding critical organs [43, 44]. The building of a proton therapy facility at the new National Cancer Centre Singapore will provide research opportunities to clinically validate the benefit of proton therapy in optimising dose to the target site and reducing early and late radiation-induced side effects in NPC patients. The present study serves as a resource for comparative analysis of the proton therapy in treatment of NPC.

CONCLUSION

Submandibular gland volumetric shrinkage persisted in NPC patients two years after IMRT. Xerostomia levels remained significantly higher, and salivary flow rates and resting salivary pH remained significantly lower, suggesting that study participants were still at risk for hyposalivation-related oral diseases.

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390 **Table 1. Study participants' baseline characteristics.**

Demographics		**n (%)**
Age (years)		50.2 (27.1 - 69.3)
Sex	Male	21 (87.5)
	Female	3 (12.5)
Ethnicity	Chinese	24 (100)
Smoking history	No	11 (45.8)
	Yes	5 (20.8)
	Previous smoker	8 (33.4)
Alcohol consumption	Yes	13 (54.2)
	No	11 (45.8)
Betel nut chewing habit	No	24 (100)
Tumour/treatment characteristics		
Tumour Stage Grouping (AJCC[†])	I	1 (4.2)
	II	7 (29.2)
	III	11 (45.8)
	IV	5 (20.8)
T classification	1	4 (16.7)
	2	12 (50.0)
	3	6 (25.0)
	4	2 (8.3)
N classification	0	2 (8.3)
	1	9 (37.5)
	2	8 (33.4)

	3	5 (20.8)
Treatment	Radiotherapy only	7 (29.2)
	Radiotherapy and chemotherapy	17 (70.8)

Data are median (range) for age; number of participants (%) or mean (standard deviation)

[†]AJCC = American Joint Committee on Cancer

Table 2. Mean tumour, salivary glands and oral cavity radiation doses.

	Mean (SD)
Tumour dose (Gy)	70[†]
Right parotid gland (Gy)	38.2 (4.7)
Left parotid gland (Gy)	39.0 (5.6)
Right submandibular gland (Gy)	64.6 (3.3)
Left submandibular gland (Gy)	65.3 (2.8)
Oral cavity (Gy)	44.5 (3.8)

[†]All patients were prescribed a tumour dose of 70 Gy.

SD = standard deviation.

Table 3. Effect of radiotherapy on clinician-rated and patient-reported xerostomia scores of study participants at all study visits.

	Pre-RT	Mid-RT	Post-RT-2w	Post-RT-3m	Post-RT-2y	
n	**24**	**22**	**22**	**22**	**15**	
†Clinician-rated xerostomia score (%)						
0	100	0	0	0	0	
1	0	50	54.5	45.4	40	
2	0	50	45.4	36.4	53.3	
3	0	0	0	18.2	6.7	
4	0	0	0	0	0	
‡Patient-reported xerostomia (XQ) score						**Overall p-value***
Mean ± SD	15.4 ± 18.1[abcd]	53.2 ± 22.3[a]	47.2 ± 25.2[b]	47.2 ± 22.5[c]	39.1 ± 24.9[d]	< 0.001

RT = radiotherapy; Post-RT-2w = 2 weeks post-RT; Post-RT-3m = 3 months post-RT; Post-RT-2y = 2 years post-RT.

SD = standard deviation

†Radiation Therapy Oncology Group/European Organization for the Research and Treatment of Cancer radiation morbidity scoring criteria (Cox et al. 1995)

‡Eisbruch et al. (2001).

[a-d]Values with same superscript in row are significantly different ($p < 0.05$).

*p-value for time effect in linear mixed model.

Table 4. Effect of radiotherapy on salivary characteristics of study participants at all study visits.

	Pre-RT	Mid-RT	Post-RT-2w	Post-RT-3m	Post-RT-2y	Overall p-value*
n	**24**	**22**	**22**	**22**	**15**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	
Resting saliva flow rate (mL/min)	0.67 ± 0.46^{abcd}	0.34 ± 0.22^{ae}	0.32 ± 0.28^{bf}	0.10 ± 0.09^{cef}	0.19 ± 0.12^{d}	< 0.001
Resting saliva pH	7.3 ± 0.4^{abc}	7.0 ± 1.0^{d}	6.4 ± 0.9^{a}	6.5 ± 0.7^{bd}	6.6 ± 0.6^{c}	< 0.001
Stimulated saliva flow rate (mL/min)	1.53 ± 0.81^{abcd}	0.49 ± 0.35^{ae}	0.42 ± 0.28^{bf}	0.16 ± 0.11^{cefg}	0.48 ± 0.39^{dg}	< 0.001
Stimulated saliva pH	7.8 ± 0.3^{ab}	7.3 ± 0.9^{c}	7.0 ± 0.8^{a}	6.4 ± 0.8^{bcd}	7.6 ± 0.6^{d}	< 0.001
Stimulated saliva buffer capacity†	9.8 ± 1.9^{abc}	6.0 ± 2.6^{ad}	4.5 ± 3.1^{ae}	5.0 ± 2.4^{cf}	9.9 ± 2.3^{def}	< 0.001

RT = radiotherapy; Post-RT-2w = 2 weeks post-RT; Post-RT-3m = 3 months post-RT; Post-RT-2y = 2 years post-RT.

SD = standard deviation.

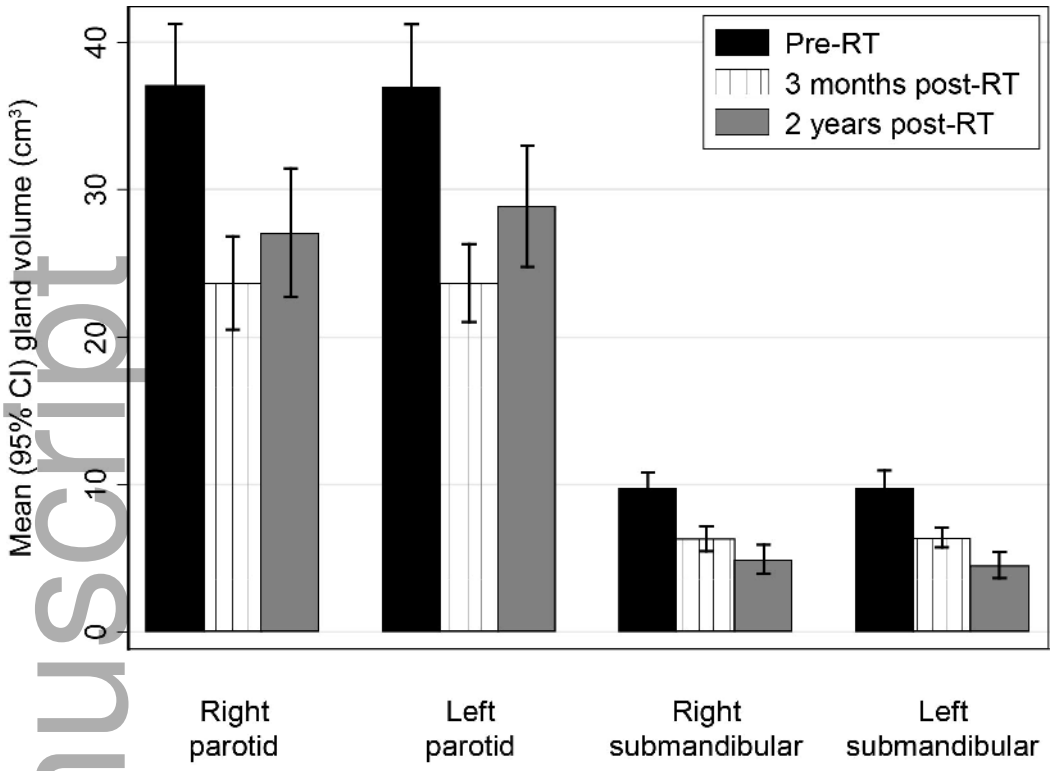
†GC Saliva-Check Buffer® kit

$^{a\text{-}f}$Values with same superscript in row are significantly different ($p < 0.05$).

*p-value for time effect in linear mixed model.

FIGURE LEGEND

Figure 1. Mean gland volumes before, three months and two years after radiotherapy. Error bars represent 95% confidence intervals (CI).



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