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ORIGINAL ARTICLE

Long-term oral effects in patients treated with radiochemotherapy for head and neck cancer

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Abstract
Purpose The purpose of this study is to assess the late oral complications and the role of salivary gland hypofunction in the severity of mucosal reaction in nonsurgical head and neck cancer patients, submitted to radiotherapy with or without chemotherapy.

Methods and materials Five hundred fifteen charts from patients treated between 2005 and 2009 were reviewed, and 41 patients met the inclusion criteria. Salivary gland function was assessed using a simplified grading system (GSX) and sialometry. Late effects were assessed using the Common Toxicity Criteria (CTC Version 2.0).
Results The average follow-up was 17.1 (4–51) months. A statistical correlation was found for whole salivary flow rates and the average CTC grades for the mucous membrane. Both unstimulated/stimulated whole salivary flow rates (<0.09 mL/min) were identified as potential risk factors ($p<0.05$) and an independent predictor for late mucous membrane toxicity (≥grade 2). A significant correlation was also found between unstimulated salivary flow rates—GSX scores ($p=0.001$) and CTC grades for salivary glands. Eighty-five percent of the patients were classified as suffering from salivary gland hypofunction, as well as 58.2 % considered dryness of the mouth the most debilitating complication.
Conclusions Considering the late effects assessed, the salivary gland hypofunction was the most significant and received the highest morbidity graduation (grade 2/grade 3); xerostomia was also considered the most debilitating complication after treatment. Data show the role of salivary gland hypofunction in the severity of late mucous membrane complication.

Keywords Radiotherapy · Chemotherapy · Late effect · Head and neck cancer · Oral complication

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Introduction

Head and neck cancer (HNC) occurs in different tissues and sites, resulting in a group of tumors with natural widespread history occurring in the same anatomical region [1] and differs in the prevalence and origin site depending on the

geographic region [2]. Two thirds of these tumors occur in developing countries, with particularly high incidence in the Indian subcontinent, followed by tropical areas of South America and South Africa [1]. Oral cancer is considered the most prevalent tumor for the head and neck area and the sixth most common cancer in the world [3, 4]. Squamous cell carcinoma (SCC) represents more than 90 % of all HNCs, and each anatomic site has its own particular spread pattern and prognosis.

Conventionally the HNC therapy is based on three modalities: surgery, radiotherapy (RT), and chemotherapy (chemo). The main challenge of RT is to control the tumor with minimum damage to the surrounding adjacent normal tissues [5]. In general, radiation treatment for HNC is administered in five fractions of 1.8 to 2 Gy, with a total dose of 66 to 70 Gy, during 6.5 to 7 weeks [6]. Combined modality chemoradiation (CRT) has been indicated in advanced cases. Cisplatin is commonly used in the treatment of HNC and is the most widely tested regimen as a single agent. Cisplatin is prescribed in a dose of 100 mg/m^2, once every 3 weeks (days 1, 22, and 43) for 2 to 3 cycles [7]. This regimen is considered the reference of chemoradiation for most adjuvant treatments of HNC according to the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) [7, 8]. In addition, when surgery is contraindicated, RT is used as a definitive treatment, combined or not with chemo, or as a palliative form [5].

There is an increase on the acceptance of altered fractionated RT and CRT. Chemotherapeutic agents are synergistic when combined with RT. As a result of this evidence, there is a clear trend on the use of nonoperative approaches particularly in pharyngeal and laryngeal cancers [9, 10]. When CRT is intensified, the probability of toxicity increases as well as the number of patients experiencing acute and late complications [11–13]. Therefore, those therapy's modalities can produce physical, psychic, and social sequelae [3].

The most frequent described late oral complications (LOC) are: salivary gland hypofunction and xerostomia, mucosal fibrosis and atrophy, trismus, taste alterations, dental caries (*radiation caries*), soft tissue necrosis, fungal, bacterial and viral infections, dysphagia, and osteoradionecrosis [5, 14]. Several studies have demonstrated separately these effects, and the xerostomia is the sequela most analyzed in the studies [15–17]. The true extent of the long-term adverse events is beginning to be regularly documented [9]. Moreover, it is believed that many of these studies, which report the prevalence of late effects, probably underestimated the real risk of its occurrence due to death caused by the cancer or other reasons, and also for not adding the patient to an extended follow-up program [12].

Recent papers have shown the increase on the survival rates in HNC patients and the importance to recognize the late effects in patients with compromised quality of life. Thus, the purpose of the present study was to assess the LOC and the role of salivary gland hypofunction in the severity of mucosal reaction in nonsurgical HNC patients, submitted to RT with or without chemo.

Materials and methods

Patient eligibility

Five hundred fifteen HNC patients' charts related to the period from January 1, 2005 to July 31, 2009 in the Division of Radiotherapy, Federal University of Sao Paulo (UNIFESP) were reviewed. Patients treated for malignant tumor in the oral cavity, pharynx, larynx, and unknown primary site; age ≥18; Karnofsky performance score ≥60; and treated with RT with or without chemo (at least 90 days after RT) were included in this study. The exclusion criteria were: patients submitted to surgery, patients with salivary gland and initial laryngeal cancers, and those that did not complete RT. The local ethics committee approved the study UNIFESP/CEP 0278/08, and a written informed consent was obtained from each patient.

Radiation treatment

Radiation treatment was performed with megavoltage equipment: Linac 6 MV (Varian) or telecobalt therapy—^{60}Co (Alcyon II, CGR—Mev, Varian). The patients were treated with parallel/opposed fields, which included the cervicofacial region, and a direct field for the supraclavicular fossa. Patients had all major salivary glands included in the radiation field. Primary tumors were treated with 2-Gy fractions on each of the five consecutive days, during 7 weeks, with a median RT dose of 70 Gy.

Data collection

After reviewing 515 HNC patients' charts, 41 patients met the inclusion criteria. The patients were recruited to be examined at the radiotherapy clinics.

During the patient's visit, the actual medical history was recorded and also an oral examination was performed. The clinical aspects such as individual habits, demographic characteristics and dental status concerning to dentition (use of dental prostheses, frequency of professional care, dental and periodontal diseases), tumor (site and clinical stage), and treatment parameters (protocol, dose per fraction, total dose, irradiated volume and chemo) were registered. Periodontal disease was defined as bleeding on probing associated to periodontal attachment loss.

Long-term effects assessments

Effects were assessed and scored using the Common Toxicity Criteria (CTC) system Version 2.0—RTOG/EORTC, Late Radiation Morbidity Scale, which is found in Appendix IV of the CTC Version 2.0 (CTCAE v2.0) [18, 19]. The adverse events for mucous membrane, salivary gland, bone, joint (temporomandibular joint), esophagus, and taste were evaluated (Table 1).

Salivary flow measurement

Salivary gland hypofunction and xerostomia were graduated according to the degree of dryness in the mouth and the response to stimulus using a grading system for xerostomia (GSX) proposed by Eisbruch et al. [20] (Table 2). Sialometry was performed using the RTOG Protocol 97-09 [21]. Previously, patients were oriented not to drink or eat at least 60 min before evaluation. The sialometry was performed in the morning. Patients were seated, with eyes opened, and were instructed to minimize orofacial movements and not to swallow during the entire collection procedure. Before the collection, patients were instructed to swallow and then to accumulate saliva in the floor of the mouth for 60 s without swallowing. Patients were oriented to spit the accumulated saliva into a recipient graded in milliliters. The patients repeated this procedure four more times for a total collection time of 5 min (unstimulated sialometry). Gustatory method was used for stimulated sialometry. The technique applied for this stimulation was based on the use of a 2 % citrate solution applied to the dorsolateral borders of the tongue. First, the patient had his/her mouth empty of any saliva or mucous and then the 2 % citrate solution was applied with cotton-tipped applicators, to the lateral tongue bilaterally five times over a 2-min period (*0, 30, 60, 90 and 120 s*). Then, the same procedure was performed for stimulated sialometry, and whole saliva was collected for another 5 min after stimulation [22]. The salivary flow rate was measured in milliliters per minute, and patients presenting a mean of unstimulated whole saliva flow rates ≤0.1 mL/min and stimulated whole saliva flow rate of ≤0.7 mL/min were classified as suffering from hyposalivation.

After finishing the oral exam, patients' subjective perception for the most debilitating late effect was recorded. In accordance with the oral complication presented, patients were reoriented about the oral health recommendations such as preventive dental procedures and dry mouth care and also received an informative treatment late effects brochure. When necessary they were referred to the dental clinic.

Statistical analyses

Data were submitted to descriptive and statistical analyses. Statistical analyses were performed by the software

Table 1 RTOG/EORTC late radiation morbidity scoring scheme

Toxicity late RT morbidity scoring	Grade				
	0	1	2	3	4
Bone	No change from baseline	Asymptomatic	Moderate pain or tenderness	Severe pain or tenderness	Necrosis/spontaneous fracture
Esophagus	No change from baseline	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semisolid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required	Necrosis/perforation; fistula
Joint (temporomandibular)	No change from baseline	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis/complete fixation
Mucous membrane	No change from baseline	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucus	Marked atrophy with complete dryness; severe telangiectasia	Ulceration
Salivary glands	No change from baseline	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Other—taste disturbance (dysgeusia)	Normal	Slightly altered	Markedly altered	Taste disturbance (dysgeusia)	–

Toxicities occurring greater than 90 days after radiation therapy

Table 2 Grading system for xerostomia

Subjective
Grade 1: No disability
Grade 2: Dryness requiring additional fluids for swallowing
Grade 3: Dryness causing dietary alterations, interference with sleep, speaking, or other activities
Objective (unstimulated whole saliva)
Grade 1: Flow ≥0.2 mL/min
Grade 2: Flow 0.1–0.2 mL/min
Grade 3: Flow ≤0.1 mL/min

Proposed by Eisbruch et al.

Statistical Package for the Social Sciences (SPSS) v. 16.0 for Windows (SPSS Inc., Chicago, IL, USA). The level of significance was set at $p<0.05$. A univariate analysis was performed to determine the relationship between the variables and the CTC—RTOG/EORTC graduation and salivary flow rates. Pearson's chi-square (χ^2) and Mann–Whitney tests were used for nominal and categorical variables, respectively. A cutoff value was established (ROC curve) to the unstimulated/stimulated salivary flow rates and correlated with all CTC—RTOG/EORTC events; then, the odds ratio (OR) and relative risk were obtained. For the CTC v. 2.0—RTOG/EORTC scores, grades 0 and 1 were grouped together, as well as grades 2 and 3.

Results

The majority of patients included in the present study were males with an average age of 60.7 years and a history of smoking and/or alcoholism. The patients did not suffer from other major comorbidities. The most prevalent cancer diagnoses were SCC of the pharynx and larynx, and the patients were treated with concomitant chemoradiation. The follow-up period varied from 4 to 51 months with an average of 17.1 months and a predominance of mild LOC (grade 0–1). Late toxicity grading is shown in Fig. 1.

Considering the clinical variables (age, sex, smoking, alcoholism, hypertension, and diabetes), tumor characteristics (localization, histology, and stage), and cancer treatment (treatment modality, follow-up time), no prognostic factors were identified for the development of moderate/severe complications. Thus, no clinical/tumor/treatment variables were correlated to development of LOC, as seen in Table 3.

During oral examination it was found that 22 (53.7 %) of the patients were dentate (at least one tooth) and 19 (46.3 %) used dental prostheses (partial/full dentures). In regards to the dentate patients, nine (40.9 %) had dental caries, five (22.7 %) periodontal disease, and four (18.2 %) other dental complications (hypersensitivity or endodontic inflammation). Twenty-two (53.7 %) patients underwent dental professional care before RT, 5 (12.2 %) during RT, and 14 (34.1 %) after treatment.

Abnormal unstimulated whole saliva flow rates were identified in 33 (80.5 %) of the patients and classified as suffering from hyposalivation. The GSX grading system showed a predominance of patients with grade 2 and 3 xerostomia. The results for GSX subjective grading were 19.5 % (grade 1), 36.6 % (grade 2), and 43.9 % (grade 3), and results for GSX objective (unstimulated whole saliva) were 26.8 % (grade 1), 39.1 % (grade 2), and 34.1 % (grade 3).

A significant correlation was observed between the CTC—RTOG/EORTC system for late salivary gland complications and the GSX subjective and objective criteria. Moderate and severe complications (grade ≥2 CTC—RTOG/EORTC) for

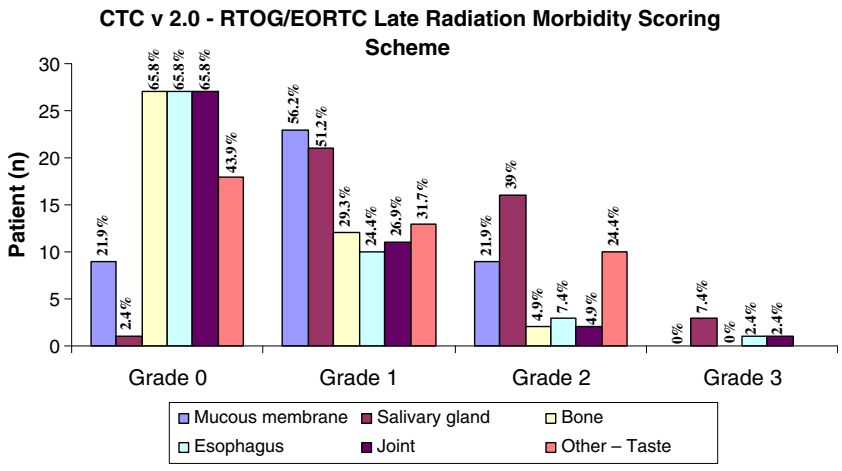

Fig. 1 CTC—RTOG/EORTC late radiation morbidity scoring scheme. *CTC* Common Toxicity Criteria, *RTOG/EORTC* Radiotherapy and Oncology Group/European Organization for Research and Treatment of Cancer

Table 3 Demographic, tumor, and treatment characteristics

Characteristics		Frequency	%
Age at exam (years)			
Mean		60.7	
Median		62	
Sex (*n*)			
Male		37	90.3
Female		4	9.7
Alcohol			
Nonalcohol user		9	21.9
Ex-alcohol user		31	75.6
Previous and actual alcohol user		1	2.5
Smokers			
Nonsmokers		6	14.7
Ex-smokers		27	65.8
Previous and actual smokers		8	19.5
Diabetic			
No		39	95.2
Yes		2	4.8
Hypertensive			
No		29	70.7
Yes		12	29.3
Primary site			
Oral cavity		2	4.9
Pharynx		27	65.8
Larynx		7	17.1
Unknown primary site		5	12.2
Stage[a]			
I–II		4	9.7
III–IV		37	90.3
Histological type			
Squamous cell carcinoma		34	82.9
Other		7	17.1
Treatment modality			
Chemoradiation		34	82.9
Radiotherapy—exclusive		7	17.1
Radiation total dose (Gy)			
70		40	97.5
50		1	2.5
Unstimulated whole saliva flow rate	Median (range), mL/min	0.12 (0–0.8)	
Stimulated whole saliva flow rate	Median (range), mL/min	0.19 (0–1.2)	

[a]TNM classification—Union for International Cancer Control

salivary glands correlated with the lower unstimulated whole saliva flow rates measured by GSX ($p=0.001$), as demonstrated in Table 4.

A cutoff value was established for both unstimulated and stimulated whole saliva flow rates (<0.09 mL), and the statistical analysis showed that low salivary flow rates may be a potential risk factor ($p<0.05$) and an independent predictor for the severity of mucous membrane late effects (grade 2 or higher). For the unstimulated whole saliva flow rates, it was found that OR=7.14, 95 % confidence interval (95 % CI)=(1.41; 36.08), relative risk (RR)=4.3, and $p=0.032$, and for the stimulated whole saliva flow rates OR=8.67, 95 % CI=(1.67; 44.94), RR=4.8, and $p=0.017$ (Table 5).

Xerostomia measured by a direct interview was present in 24 (58.2 %) patients and was also considered the most debilitating complication by the patients. Dysphagia was considered the second most debilitating finding (six

Table 4 Correlation of GSX criteria and salivary glands scored by the CTC—RTOG/EORTC system

Grade			Salivary glands		*p* value[a]
			0–1	≥2	
Subjective GSX	1	*N*	8	0	NS
		%	36.4	0.0	
	2	*N*	10	5	
		%	45.5	26.3	
	3	*N*	4	14	
		%	18.2	73.7	
Objective GSX	1	*N*	9	2	0.001[a]
		%	40.9	10.5	
	2	*N*	11	5	
		%	50.0	26.3	
	3	*N*	2	12	
		%	9.1	63.2	

GSX grading system for xerostomia, *NS* not significant

[a] Pearson's chi-square (χ^2) test

patients, 14.6 %), followed by taste alterations (four patients, 9.9 %). Only three patients (7.3 %) demonstrated no complications at the time of the examination. Temporomandibular joint and bone alterations were not reported as debilitating late effects.

Discussion

Concomitant RT/chemo plays an important role in the management of HNC patients and has potentially brought increases in survival rates for this group of patients [23, 24]. However, it is also associated with several undesired reactions and is related to increasing the development of late toxicity. Therefore, since the number of long-term survivors of HNC has increased, long-term side effects have to be considered when assessing the benefit of RT and chemo.

Table 5 Correlation of salivary flow rates (sialometry) and mucous membrane scored by CTC—RTOG/EORTC system

	Mucous membrane			
	0–1	≥2	Total	*p* value[a]
Unstimulated salivary flow rates (mL/min)				
<0.09	7	6	13	0.032
≥0.09	25	3	28	0.032
Stimulated salivary flow rates (mL/min)				
<0.09	1	6	7	0.017
≥0.09	26	3	29	0.017

[a] Pearson's chi-square (χ^2)

Chronic or late reactions can occur months and years after RT and/or chemo have finished, and the most delayed side effects occur within 3 years after the initiation of treatment [12, 25]. Comprehensive data on LOC from randomized trials of radiation therapy with or without chemo, however, are insufficient. In our review, no reference was found regarding details about most frequent LOC specifically for nonsurgical patients after treatment. We believe that rates for LOC in this group of patients may not have been often reported due to the difficulty to capture accurate information.

Several classification systems have been proposed, and late toxicity grading for radiation treatment has been currently based upon the RTOG/EORTC Late Radiation Morbidity Scale [26–31]. However, there is no consensus about the best method for quantifying the late normal tissue complication and how to group all the LOCs into a single system.

Citrin et al. [28], examined ten HNC patients, stage III or IV, treated with chemo and concurrent RT, and observed that the vast majority of RTOG late toxicities were grade 1 or 2. In view of our results, also using the CTC—RTOG/EORTC system, late adverse events in bone esophagus, and temporomandibular joint and taste alterations were not common. Overall, in an average of 17.1 months follow-up, the data showed a predominance of mild LOC (grade 0–1). However, some authors [14, 29, 32] found late esophageal injury and loss of taste as a lifelong alteration after RT/chemo.

Results could confirm a significant number of patients with moderate and severe complications (grade ≥2, CTC—RTOG/EORTC) for salivary glands and the mucous membrane. A study done by Olmi et al. [33], which evaluated different RT schedules for locoregionally advanced carcinoma of the oropharynx also reported a predominance of grade ≥2 late side effects involving the mucosa and salivary glands.

Particularly for nonsurgical patients, authors [9] have shown the predominant use of nonoperative approaches in pharyngeal and laryngeal cancers as well as in our findings. Although, some authors [34] reported that older age, advanced T stage, and larynx/hypopharynx primary site were strong independent risk factors for severe late toxicity after concurrent chemoradiation. In our univariate analysis, no clinical/tumor/treatment prognostic factors were found to be significantly associated with the development of moderate/severe LOC. However, the limitation of our study is that most patients were treated for advanced stage cancer with high total radiation doses. Therefore, we cannot assess to what extent tumor/treatment factors are associated to LOC, since we do not have a range of patients with different stages/therapeutic modalities.

Twenty-two (53.6 %) out of the 41 patients submitted to RT and/or chemo and underwent dental professional care prior to treatment. As opposed to this finding, we verified

that 34.1 % has not maintained oral care after treatment. During examination, dentate patients (53.6 %) presented dental caries and periodontal diseases, respectively 40.9 and 22.7 %. Although these complications have been frequently reported, there is still a discussion for understanding the dental caries development either due to direct influence of radiation or secondary to salivary gland dysfunction. It has been suggested that RT may induce alterations in the composition of saliva due to decrease in secretory immunoglobulin A, pH, and bicarbonate concentration, creating an appropriate environment for cariogenic microbial development [35]. Moreover, the risk of periodontal infection is increased due to radiation-induced hyposalivation, the concomitant increased plaque accumulation, increased collagen synthesis resulting in fibrosis, and alteration in oral microflora [32, 36].

Xerostomia has been reported to be the most common late side effect in many patients treated with RT and/or chemo for HNC [37, 38]. Our findings were consistent with earlier reports [5, 14, 39, 40], which highlighted late xerostomia as a complication occurring with moderate to severe graduation (grade 2, grade 3) and high incidence of 80.5 % in a range of 77.8 to 93 %. These findings evidence the importance of these sequelae and that efforts should be made to prevent and manage it in patients.

It remains difficult to connect the symptoms with the measured salivary flow rates. The subjective feeling of dry mouth does not necessarily correlate with objective measurements of salivary gland function [17]. For this reason we used the Eisbruch et al. [20] assessment and reporting of xerostomia which includes both subjective symptoms and objectively measured saliva secretion (sialometry). The system was proposed by the authors to set a clear endpoint for trials of post-RT xerostomia, which is associated with clinically relevant functional difficulties. In accordance with this system, studies report the whole-mouth unstimulated saliva flow rates in patients having <0.1, 0.1 to 0.2, and >0.2 mL/min correlating roughly with symptoms [41]. In accordance with the literature, our study showed a significant correlation between the moderate and severe complications (grade ≥2) for salivary glands using the CTC—RTOG/EORTC system with the GSX objective criteria (lower salivary flow rates, $p=0.001$).

The role of salivary gland hypofunction in the oral late complication is a matter of debate. Complications induced by hyposalivation include alterations in the oral soft tissues, shift in oral microflora, hyposalivation-related dental caries and periodontal disease, and mucosal alterations such as inflammation, atrophy, and ulceration [42].

It has also been suggested that salivary gland dysfunction may have an influence in the severity of mucosal impairment. In an earlier study [43], oral mucosal alterations were evaluated in different salivary gland hypofunction groups, and it was reported that the postradiation group showed the highest frequency of oral mucosal alterations (94 %). Our results showed a statistical significance ($p<0.05$) between salivary gland hypofunction and the severity of late mucosal alteration. At the same time, it is important to emphasize that in this group, patients received in both salivary glands and mucous membrane a high dose of radiation, and thus, both have a high level of damage. However, the low cutoff values of 0.09 mL/min for both unstimulated and stimulated whole saliva flow rates may suggest that patients with the highest risk of severe late oral mucous membrane toxicity present an important late radiation-induced destruction of salivary gland tissue with limited residual secretory capacity. Thus, if salivary stimulatory effects are insufficient in this group of patients, the symptomatic management of the salivary gland hypofunction and lubrication of the oral mucosa, with pharmacological, gustatory, or masticatory stimulation, should be indicated by frequent application of water or oral mucosal lubricants/saliva substitutes. While this may provide some relief of xerostomia, they lack the protective effects of saliva, although some of them contain fluoride and electrolytes to prevent demineralization of the teeth [44].

It is still an open question whether the prevalence of late oral complications can also be attributed to chemotherapy [17, 37]. It was recently suggested that the mucosal changes specially induced by chemo are usually acute, and healing occurs within weeks of cessation of cytotoxic chemo. In contrast, RT induces acute and chronic changes in the oral mucosa as a result of epithelial atrophy, fibrosis of connective tissues, neurologic sensitization, and/or neuropathy, which may also predispose oral tissues to ulceration following trauma or injury [16, 35].

The patients' perception for the most debilitating late complication has been reported only for mucosal acute reactions [45]. However, a clear understanding of the patients' most debilitating experience after treatment is not available in quality of life studies. Our data showed that mouth dryness (xerostomia) is the most debilitating LOC (58.7 % of patients), as well as we reinforce that patient's perception is relevant to better recognize whether or not some other symptom is also involved with xerostomia or if it is a distinguished effect. This is important because as soon as the most debilitating effect is recognized, the adequate care can be applied, optimizing the treatment.

Regardless of limitations in this study, we recognize that the limited number of patients made our evaluation difficult. However, only nonsurgical patients were included for controlling the bias of including surgical patients. In this case, the normal tissue response to RT/chemo could be affected by the surgery sequelae such as limited mouth opening, esophagus dysfunction, pain, and salivary glands removal. Moreover, there is a potential to reduce toxicity using more

anatomically targeted radiation delivery technologies, biologically targeted drugs, and growth factors. Unfortunately, these approaches are not widely available especially in developing countries.

Overall, our data showed that salivary gland hypofunction was the most significant late effect with the highest morbidity graduation (grade 2/grade 3), and it was considered the most debilitating complication after treatment. Results also suggest the importance of the role of salivary gland hypofunction for the severity of late mucous membrane complication. It clearly indicates the relevance of detecting and managing salivary flow rates for oral mucosal hydration and thus to potentially reduce late mucosal injuries.

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Conflict of interest The authors report no actual or potential conflict of interest.

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