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ORIGINAL ARTICLE

A prospective study on oral adverse effects in head and neck cancer patients submitted to a preventive oral care protocol

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Abstract

Objective To evaluate the occurrence and severity of oral complications, number of radiotherapy (RT) interruptions and quality of life (QoL) in a population of head and neck cancer patients receiving a preventive oral care program (POCP) and photobiomodulation therapy (PBMT).

Methods Prospective cohort of 61 head and neck cancer patients undergoing radiochemotherapy were monitored and submitted to a POCP that included oral hygiene and plaque control, removal of infection foci, dental restorations, periodontal therapy, fluorotherapy, oral hydration, and denture removal at night, combined with daily PBMT. Outcomes included occurrence of adverse effects such as severity of oral mucositis (OM) and oral symptoms (pain, solid and fluid dysphagia, odynophagia, dysgeusia), quality of life impacts, and interruptions of radiotherapy (RT) due to symptoms. Disease-free and overall survival rates were evaluated.

Results There was a significant improvement in oral health conditions between initial assessment and the two longitudinal assessments ($p < 0.05$), which indicates that the POCP was effective for plaque control and reduction of gingival inflammation. All participants were free of OM at the beginning of the RT regimen and only 45.9% after the 7th session, and few patients ranked the highest score of OM. For all symptoms related to OM, there was a progressive increase of severity until the 14th RT session, which remained stable until the completion of the RT regimen. The same effect was observed for the quality of life measures. Discontinued RT due to OM occurred in only three patients (5%), and the maximum duration was 10 days. The overall survival rate was 77% and disease-free survival was 73.8%. Lower survival time was observed for patients with no response to RT ($p < 0.01$).

Conclusions The findings of this study suggest a positive effect of an oral preventive care program for head and neck cancer patients submitted to RT. The PBMT associated with a rigorous POCP resulted in satisfactory control of oral adverse effects, reduction of quality of life impacts, and interruption of RT regimen due to severe OM.

Keywords Head and neck neoplasms · Preventive dentistry · Mucositis · Radiotherapy · Quality of life

Introduction

Oral adverse effects are common in patients with head and neck cancer (HNC) receiving radiotherapy (RT) and/or chemotherapy (CT) and are associated with increased morbidity and mortality [1]. Patients undergoing RT are highly susceptible to develop severe oral mucositis, which may lead to serious impairment on oral function and comfort that may contribute to derangement of patient's overall health condition. As a consequence, reduction or interruption of the radiochemotherapy regimen may be necessary, compromising its therapeutic effectiveness [2, 3]. Treatment delays in

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completing RT for many neoplasms are considered a major problem affecting treatment outcome in HNC patients [2].

The most adverse effect is the OM that affects 90% of patients with oropharyngeal cancer [1]. OM is associated with pain, dehydration, malnutrition, and loss of quality of life [4]. It is the main cause of discontinuation of RT, together with other symptoms such as odynophagia, dysphagia, and dermatitis [5].

Studies showed that the incidence and severity of oral symptoms associated with RT and CT can be reduced by effective preventive oral care measures [5–10]. The priority of a preventive oral care protocol (POCP) is the elimination of infection foci, restoration of caries lesions, and periodontal therapy [11]. These preventive measures have been used alone or in combination with other procedures such as the use of topical anesthetics, analgesics [12], anti-inflammatory and antimicrobial drugs [13]; photobiomodulation therapy (PBMT) [6, 14], and antiseptic mouthwash [6].

The use of PBMT has shown interesting results in the treatment of oral complications of cancer patients, in special for OM. Previous studies of our research group showed that the use of red laser is associated with a reduction in the inflammatory process, evoking less intense symptoms [14, 15]. The benefits of PBMT in HNC included improvement in the quality of life [16, 17], reduced pain and incidence and severity of mucositis, lower occurrence of dysphagia [18] and increased salivary flow [19]. Low-level laser therapy used for patients with oral mucositis also increases salivary output through indirect stimulation of minor and major salivary glands. The exact mechanisms responsible for such effects on salivary tissue remain poorly understood and are probably associated with stimulation of growth factor releasing and cytokinesis [19].

A retrospective cohort study in head and neck cancer patients submitted to RT assessed the level of patient adherence to oral preventive measures and its impact on cancer treatment [5]. Findings showed that patients with higher adherence to the oral preventive measures had higher rates of RT completion and higher overall survival rates, which suggest that oral care may contribute to improve the prognosis of treatment by reducing the negative impact of oral complications [5]. However, methodological weakness inherent to the retrospective design, differences in the baseline characteristics of the study groups, and lack of standardized procedures in oral care and data collection limit the generalizability of the findings.

Therefore, this study aimed to describe the occurrence and severity of oral complications, the number of RT interruptions, and QoL in a population of HNC patients receiving POCP and PBMT. The study hypothesis was that HNC patients receiving the combined provision of routine oral preventive measures and photobiomodulation therapy as adjuvant care alongside the RT protocol would present lower levels of oral complications—especially OM, lower impacts on oral-related quality of life, and lower episodes of interruption of RT regimen due to oral symptoms. These effects may ultimately have also a positive effect on patient overall cancer treatment outcomes.

Material and methods

Sample

The present article is reported according to the STROBE statements (https://www.strobe-statement.org) [20] that aims to improve the quality of observational study reports. This prospective observational study was conducted in the Araujo Jorge Hospital (Association of Combat Cancer in Goias), in Goiania, Brazil, and was approved by the local research ethics committee (approval no. 012/12). All participants were regular patients of the HNC service, and received POCP and PBMT treatments as part of their routine overall cancer treatment. Participants were recruited between February 2016 and December 2017, and patient assessment and data collection was finished in April 2018.

The sample comprised patients diagnosed with squamous cell carcinoma (SCC) in the head and neck region and submitted to RT or in combination with CT. The HNC region comprised the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx. All included participants were required to have a performance status rated as score ≤ 2 according to the Eastern Cooperative Oncology Group [21]. Performance status is a score that estimates the patient's ability to perform certain activities of daily living without the help of others, in order to assess how a disease is progressing, how the disease affects daily living abilities, and to determine appropriate treatment and prognosis for oncological patients [21].

There was no restriction for inclusion regarding the clinical stadium of the tumor (Union for International Cancer Control), except for cases of laryngeal tumors with tumor extension (T) between 1 and 2, which were excluded since the radiated area was remote from the region of interest.

All participants received an RT regimen greater than 60 Gy at the primary lesion site (2 Gy/day), 5 days per week. Patients who received a daily dose of RT exceeding 2 Gy were excluded.

Participants' demographic data and clinicopathological features were recorded, such as cancer risk factors, location, clinical stadium and histological grade, performance status, and treatment modalities. Oral health conditions were assessed by clinical examination and, in case of other transdisciplinary supportive care needs (nutritional, psychological, social work, phonetic therapy, and others), patients were properly referred and all procedures were recorded in the patient's medical charts.

Preventive oral care program

Participants were enrolled in a POCP that included prophylactic treatment for minimization of RT-induced OM and other side-effects of RT. POCP protocol included daily monitoring of oral hygiene, removal of infection foci, restoration of caries lesions and cavities, periodontal therapy, fluorotherapy, oral hydration, and partial/complete denture removal at night, combined with daily PBMT. The POCP was performed throughout the complete RT/CT treatment.

The standard oral examinations were performed when patients consented to participate in the study (1st evaluation), at the first RT session (2nd evaluation), and the 15th RT session (3rd evaluation).

Oral health was assessed using the Oral Assessment Guide (OAG) [22], Periodontal Screening and Recording (PSR) [23], and Plaque Control Record by O'Leary [24]. The OAG is an instrument for assessment of oral health of H&N cancer patients with eight categories (voice, ability to swallow, lips, saliva, tongue, mucous membrane, gingiva, and teeth) for which are assigned an ordinal score of 1 (normal or unchanged), 2 (mild to moderate change) or 3 (moderate to severe change). A summative score was obtained ranging from 8 to 24.

The periodontal condition was assessed based on the PSR score [23], by probing the gingival sulcus using a standardized probe with a 0.5-mm spherical tip and a colored band extending from 3.5 to 5.5 mm from the tip of the probe. The mouth was divided into sextants and a total of six points on each tooth were examined in all remaining teeth. The highest score in each sextant was recorded on an scale ranging from 0 to 4 (0 = absence of clinical signs; 1 = bleeding; 2 = gingival calculus and/or defective restoration margin; 3 = colored band on probe partially intrasulcular; 4 = colored band in interior of periodontal pocket; and code * periodontal abnormalities), and the worst finding in each sextant determines the PSR score.

The biofilm was measured using the Plaque Control Record proposed by O'Leary [24]. A 1% basic fuchsin solution was used for plaque disclosing, and a percentage index was obtained by calculating the ratio of the total number of teeth surfaces with plaque and the total number of faces examined.

Photobiomodulation therapy

Participants received daily sessions (5 days per week) of PBMT with an indium gallium arsenic phosphate diode laser (InGaAIP, Twin Flex Evolution, MMOptics Ltd., São Paulo, Brazil), 25 mW power and 660 nm wavelength (red laser), continuous, punctual, with an energy density of 6.2 J/cm^2 per point, and at an approximate distance of 1 cm. Irradiated point received 0.24 J of energy for 10 s to an area of 0.04 mm^2 at each area of interest. The total energy of the PBMT for each patient was 14.88 J/day (620 s/session per patient). The PBMT protocol was based on Oton-Leite et al. [15].

Laser applications were performed all through the oral cavity, distributed in ten points on the lateral border of the tongue and mucosa, four points on the labial mucosa, three points on the dorsal tongue, two points on the floor of the mouth, five points on the soft palate, and one point in the labial commissure, comprising a total of 62 points distributed 1 cm apart in the oral cavity and oropharynx, with the exception of the tumor area.

Outcomes

Adverse effects

The severity of OM, loss of taste, dysphagia, odynophagia, and dysgeusia were evaluated before the first RT and in the 7th, 14th, 21st, and 30th RT sessions. The degree of OM was assessed according to the National Cancer Institute (NCI) scoring criteria: 0—no changes; 1—erythema; 2—pseudomembranous plaques less than 1.5 cm at the widest point; 3—confluent pseudomembranous greater than 1.5 cm in diameter; and 4—necrosis and/or deep ulceration or bleeding not induced by trauma. In addition, the World Health Organization (WHO) scale was also used: 0—no clinical change; 1—erythema and pain; 2—erythema, ulcers, difficulty eating; 3—ulcer and liquid diet; and 4—the impossibility of eating.

The occurrence of pain, dysgeusia, dysphagia, and odynophagia was assessed using the "Patient Reported Oral Mucositis Symptom Scale" (PROMS) [25]. The PROMS consists of 10 items concerning mouth pain, difficulty speaking, restriction of speech due to wounds in the oral cavity, difficulty in eating solid foods and liquids, restriction on food, difficulty and restriction of drinking, difficulty in swallowing, and dysgeusia. Patient responses were recorded on a visual analogue scale ranging from 0 to 100. A summative score was obtained for measuring the impact of oral adverse effects on the patient's quality of life.

The severity of xerostomia was evaluated using the Xerostomia Inventory (XI) at the 30th RT session [26]. The XI is a multi-item approach to measuring dry mouth that comprises 11 items that assess experimental and behavioral aspects of xerostomia, measured on a Likert-type scale (never, rarely, occasionally, frequently, or very frequent), and an overall severity score for xerostomia ranging from 11 to 55.

Oral health-related quality of life

Oral health-related quality of life (OHRQoL) was assessed using the Oral Health Impact Profile (OHIP-14) [27]. The OHIP-14 is a 14-item questionnaire comprising

six domains: functional limitation, physical pain, psychological discomfort, and physical, psychological, and social disability. Items are scored on a five-point Likert scale (never, rarely, sometimes, often, and always), and a weighted summative score is obtained. All instruments used for outcome measurement were applied at baseline and the 7th, 14th, 21st, and 30th RT sessions.

Radiotherapy interruption and patient survival

The occurrence of discontinuation of the prescribed RT, and duration and reasons for RT interruption were also recorded. Patients' disease-free and overall survival rates were assessed throughout the treatment and at the post-treatment follow-up.

The complete flowchart of the study phases, outcome measures, and time points for patient assessment are depicted in Fig. 1.

Statistical analyses

Data distribution was tested for normality, and descriptive analysis was performed using frequency for categorical variables and mean/median and standard deviation for continuous variables. Non-parametric Wilcoxon test was used for within-group comparisons of the longitudinal data. Disease-free and overall survival rates were evaluated using Kaplan–Meier and the log-rank test was used. The IBM-SPSS 24.0 software was used for data analysis and the level of statistical significance was set at $p < 0.05$.

Results

During the study period, between 2016 and 2017, a total of 545 consecutive individuals were diagnosed with HNC and RT was prescribed for 449 of them. Sixty-one patients met the inclusion criteria for this study. The mean age was 58.6 (SD = 9.9), 49 (80.3%) were male, 52 (85.2%) were smokers, and 44 (72.1%) were alcohol consumers weekly, in general, more than 5 alcohol units per day. The clinic-pathological features are summarized in Table 1. All participants received transdisciplinary health team support during treatment, such as nutritional support (70.5% of participants), psychological support (54.1%), and speech therapy (11.5%).

Regarding oral condition, 54.1% were partially edentulous and 44.3% were fully edentulous. The results of the oral health assessment (OAG, Plaque Control Record, and PSR) in the three time points (after consented to participate, at the first RT session, and the 15th RT session) are shown in Table 2. For most of the measured variables, there was a significant improvement in oral health conditions between initial assessment and the two longitudinal assessments ($p < 0.05$), which indicates that the POCP was effective for plaque control and reduction of gingival inflammation (Table 2). All participants had dysphagia (liquid and solid), and OM was the main adverse effect (96.7%).

The distribution of the degrees of OM according to the number of RT sessions is represented in Fig. 2, according to the NCI and WHO. All participants were free of OM at the beginning of the RT and only 45.9% after the 7th session. The higher incidence of grades 1 to 3 occurred from the 14th session and remained almost stable until the 30th session—

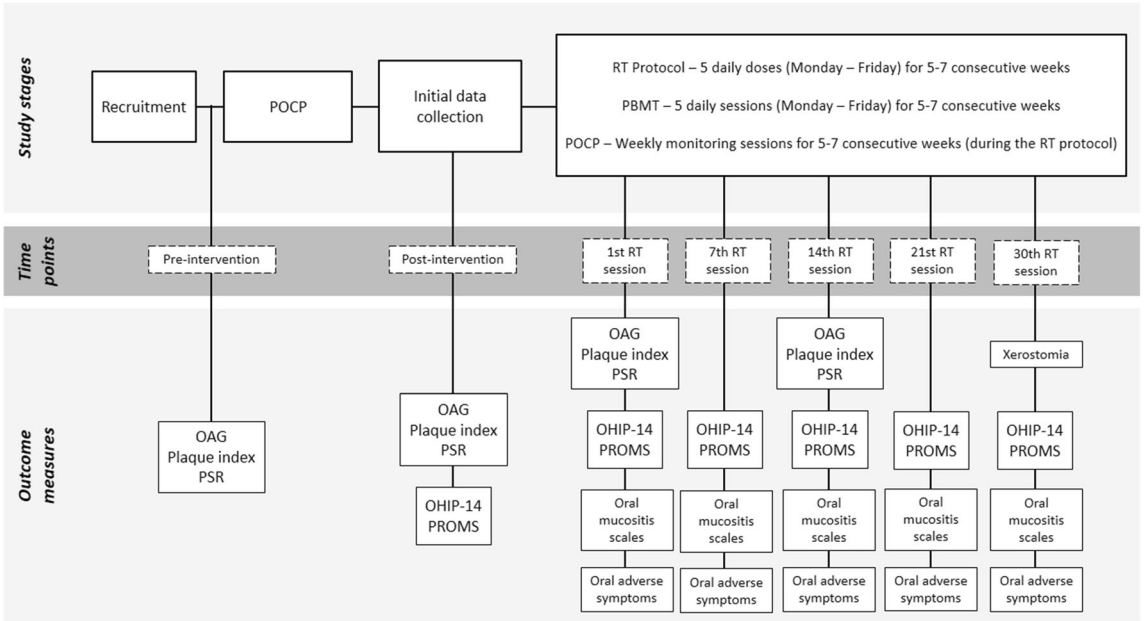

Fig. 1 Flowchart of the study phases, outcome measures, and time points for patient assessment

Table 1 Clinic-pathological features and cancer treatment protocol

Characteristic	Categories	*n* (%)
Location of the tumor	Oral cavity	14 (23.0)
	Oropharynx	30 (49.2)
	Pharynx	16 (26.2)
	Hidden primary	1 (1.6)
T Stage (participants without distant metastasis)	T1-T2	11 (18.0)
	T3-T4	49 (80.3)
	Unknown stage	1 (1.6)
N Stage	N0	22 (36.1)
	N^+	39 (63.9)
Surgical treatment		23 (37.7)
Neck dissection		22 (36.1)
Histological grade of malignancy	Grade 1	6 (9.8)
	Grade 2	38 (62.3)
	Grade 3	14 (23.0)
	No specified	3 (4.9)
Surgical margins	Free	17 (27.9)
	Exiguous	1 (1.6)
	Committed	2 (3.3)
	No evaluable	2 (3.3)
	Incisional biopsy	39 (63.9)
Cancer treatment protocol	RT exclusive	1 (1.6)
	RT adjuvant	8 (13.1)
	RT/CT	35 (57.4)
	Surgery/RT/QT	17 (27.9)
RT planning	Two-dimensional	14 (23.0)
	Three-dimensional	47 (77.0)
Number of RT sessions*		8 (±12)
RT dose (Gy)*		67 (±7)
Induction CT	TPF (docetaxel + cisplatin +5-fluoracil)	13 (86.7)
	Docetaxel + cisplatin	1 (6.7)
	5-fluoracil + cisplatin	1 (6.7)
Concomitant CT	Cisplatin	51 (98.1)
	Carboplatin	1 (1.9)
Interval of Concomitant CT cycles*	Weekly	14 (26.9)
	3 cycles every 21 days	38 (73.1)
Number of cycles of concomitant CT*	Week	6 (2.7)
	3 cycles every 21 days	2.6 (0.7)
Completion of concomitant CT prescription*		33 (62.3)

*Mean and standard deviation

RT radiotherapy, *CT* chemotherapy

mean OM scores ranged from 1.79 to 2.1 (NCI) and from 1.75 to 2.0 (WHO) from the 14th to the 30th RT session. A slight increase was observed in the last RT session for the NCI ($p = 0.039$) and WHO ($p = 0.074$) criteria. Only one patient (1.6%) ranked the highest score (score 4) at the 21st RT using the NCI criteria, and 17 patients (27.9%) ranked the highest score (score 3) on the 30th using the WHO criteria for the assessment of OM. Nevertheless, ulcerations remained without progression from the 14th until the 30th RT session.

Regarding the degree of OM, regardless of the classification, there was no association with clinical-pathological data, risk factors, modality of treatment, attendance, and oral health conditions. Increased cycles of chemotherapy combined with RT were associated with a lower degree of OM grade 2 ($p < 0.01$). Interruption due to OM (NCI) occurred in only

Table 2 Oral health assessment before, during, and after the preventive oral care program (POCP) according to the oral assessment guide (OAG), Plaque Control Record, and periodontal screening and recording (PSR). Data are expressed as median (and interquartile range)

		1st examination (after consent to participate)	2nd examination (1st RT session)	3rd examination (15th RT session)
OAG		10 (2.0)	10 (4.0)	12 (2.0)*
Plaque Control Record		68.0 (34.9)	55.7 (37.9)*	50.0 (39,1)*
PSR score (by sextant)	S1	2.0 (2.0)	1.0 (3.0)	1.0 (3.0)
	S2	2.0 (3.0)	1.0 (2.0)*	0.0 (1.0)*
	S3	2.0 (2.0)	1.0 (3.0)	1.5 (3.0)
	S4	2.0 (1.0)	1.0 (2.0)*	1.0 (2.0)
	S5	2.0 (1.0)	1.0 (2.0)*	1.0 (1.0)*
	S6	1.0 (2.0)	0.0 (2.0)*	0.0 (1.0)*

*Statistically significant difference (Wilcoxon test)—1st examination compared with the 2nd and 3rd examinations

three patients ($p < 0.01$). Other factors were not statistically significantly associated with the degree of OM using both the WHO or NCI.

Longitudinal changes in the intensity of symptoms associated with RT are in Table 3. For all symptoms related to OM, there was a progressive increase of severity until the 14th RT session, which remained stable until the completion of the RT regimen. The same effects were observed for the OHRQoL measures using both the PROMS and OHIP-14 instruments, and an overall decrease in quality of life was discrete. Xerostomia was reported by 44.3% of the patients, and the overall mean score at the last RT session was 32.8 (± 10.14), ranging from 14 to 54. However, no inference could be made since xerostomia was not assessed at baseline.

Interruption of RT occurred in 55 participants (90.2%) due to several reasons, as described in Table 4. The duration of the 107 interruption events ranged from 0 to 42 days (mean = 8.8;

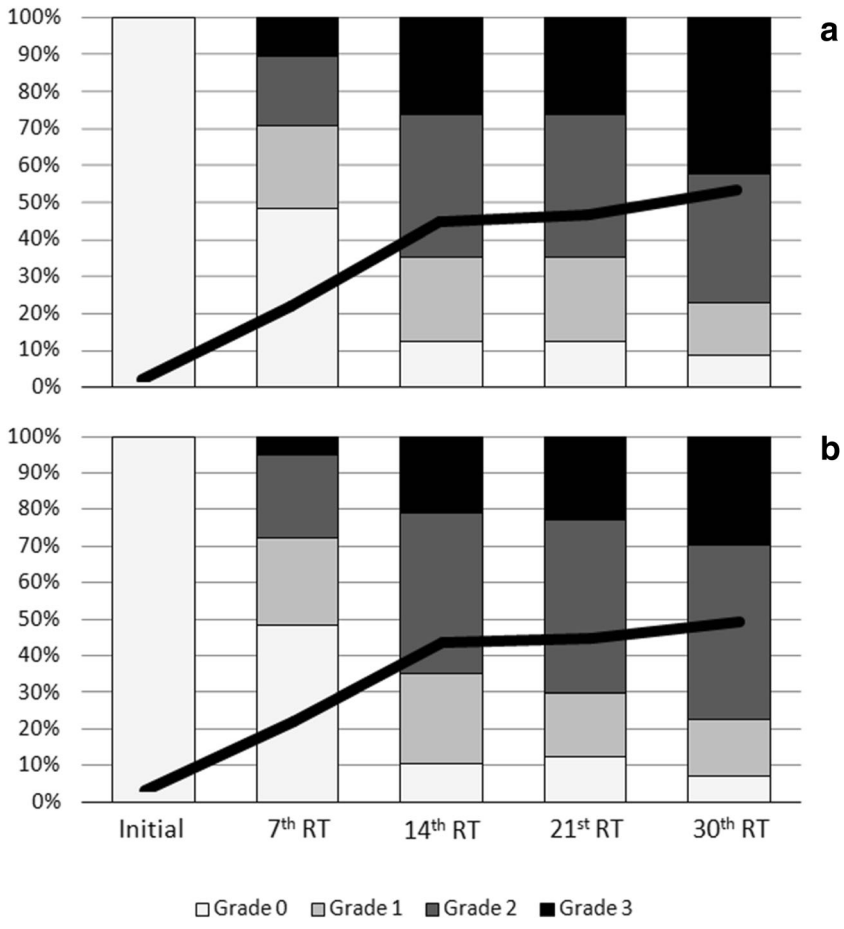

Fig. 2 Changes in oral mucositis scores according to the National Cancer Institute (A) and the World Health Organization (B). Bars represent percent of cases in each OM grade and the continuous lines represent mean values for each stage of the RT regimen (score range from 0 to 3 for WHO and 0–4 for NCI scales)

Table 3 Median (and interquartile range—IQR) scores of the quality of life measures and symptoms associated with oral mucositis throughout the RT regimen

	Scale range	RT sessions				
		Initial	7th	14th	21st	30th
PROMS	0–100	0.0 (10.0)	10.0 (23.0)*	21.5 (28.0)*	23.5 (30.0)	28.3 (30.0)
OHIP-14	0–28	2.3 (5.5)	5.1 (9.2)*	7.1 (8.3)*	5.8 (10.2)	6.0 (10.0)
Solid dysphagia	0–10	0.0 (0.0)	0.0 (7.0)*	5.0 (10.0)	6.0 (10.0)	2.5 (10.0)
Liquid dysphagia	0–10	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (4.0)	0.0 (3.0)
Dysgeusia	0–10	0.0 (5.0)	5.0 (8.0)*	10.0 (5.0)*	10.0 (2.0)*	10.0 (2.0)
Odynodysphagia	0–10	0.0 (0.0)	0.0 (3.0)*	1.2 (5.0)*	1.5 (5.0)	2.7 (7.0)
Pain	0–10	0.0 (0.0)	0.0 (3.0)*	0.3 (5.0)	0.0 (5.0)	0.7 (5.0)

*$p < 0.05$—Wilcoxon test for pairwise comparison between each RT session and the previous session

DP = 9.2). Discontinued RT due to OM occurred in only three patients (5%), and the maximum duration was 10 days.

Overall survival rate was 77% (mean survival of 35.0 months; 95%CI = 21.2–48.7), while disease-free survival was 73.8% (mean = 42.2 months; 95%CI = 29.2–55.2). Shorter survival was observed for patients who had no response to RT (disease-free survival = 31.3%; $p < 0.01$, and overall survival = rate of 31.3%; $p < 0.01$). No significant associations were found for other clinicopathological factors, such as time from diagnosis to surgical treatment, the histological grade of malignancy, regional metastasis, and the number of RT interruptions.

Discussion

The results of this study corroborate the findings of a retrospective study that included a cohort of oral cancer patients submitted to RT [5], which assessed patient adherence to oral preventive measures and its impact on treatment outcomes. Findings suggested that patients with higher adherence to preventive measures were more likely to accomplish the planned RT protocol and to have higher survival rates [5]. However, the limitations inherent to retrospective study designs, particularly the appropriate control of potential confounders and the validity of patient outcome measures, reinforce the need for prospective study designs. Hence, this study aimed to provide evidence of the benefits of a POCP associated with PBMT to minimize oral complications due to RT/CT treatment and improve disease prognosis by reducing the negative impact of these oral complications.

Table 4 Frequency of reasons for interruption of RT

Reasons	*n*
Technical problems with the RT devices	50
Fatigue of the patient	12
No transport to the hospital available	15
Side effects of chemotherapy	7
Pneumonia	7
Scheduling conflicts	7
Oral mucositis	3
Odynophagia/dysphagia	2
Advanced disease progression	2
Not registered	2

To our knowledge, this is the first prospective study to assess the outcomes of a combined POCP/PBMT protocol, in which patients were under daily monitorization and preventive interventions, to control of side effects of RT (OM, pain, dysphagia, odynophagia, and xerostomia), as well as the incidence of RT interruptions related to oral symptoms, and the impact of oral symptoms on quality of life. Findings showed that oral the incidence and severity of adverse effects and quality of life impacts were lowered and tended to remain stable during the second half of the RT regimen (between the 14th to the 30th RT session). These positive effects were associated with a low incidence of RT interruption due to symptoms and high RT conclusion rates.

The prospective design also allowed a rigorous control of patient assiduity to the scheduled appointments and adherence to the POCP. Mean patient attendance rates were 86.7% (± 16.84) and probably were positively affected by the daily supportive oral care provided by the dental team.

Due to ethical reasons, there was no control group in our study. Although it is a major limitation of the study design, the PBMT and POCP are part of the treatment protocol of the hospital. From the ethical perspective, it would be unethical not providing any of these interventions for the participants of the study in a control group. The use of a convenience sample and the relatively small number of participants were also limitations of this study. This is partially explained by the difficult adherence of patients in the cancer treatment protocol and the preventive program on a daily basis.

There are evidence from the literature that oral care measures reduce the incidence and the severity of OM in HNC patients submitted to RT [6, 8]. A retrospective study with patients submitted to hematopoietic stem cell transplantation

also reported a reduced incidence of OM when associated with oral hygiene measures [28]. Similarly, lower incidence of OM was found in pediatric patients in an intensive care unit when preventive oral care measures were adopted [29]. The positive effect of PBMT in reducing the incidence of OM grades 3 and 4 in HNC patients submitted to RT and CT was also reported [16]. Our results showed that 96.7% of the participants had some level of OM. However, from those patients presenting OM grade 2 and 3 only three patients had interruptions in the RT protocol, and no patient with OM grade 3 in the 30th RT session discontinued RT. In addition, more than 90% of the participants completed their RT with quality of life at acceptable levels.

Since PBMT has been proven to provide beneficial effects in the control of OM, all participants received the same POCP combined with daily PBMT. There is sound evidence that PBMT acts to reduce the incidence, duration, and severity of OM [18, 30]. Gautam et al. [18] in their studies showed a reduction in the incidence and duration of OM in patients with RT and CT in the oral cavity, oropharynx, and pharynx. Elderly patients, submitted to RT in the head and neck region, presented a reduction in the incidence of severe OM [30]. Prophylactic laser therapy also reduced the incidence, duration, and severity of OM in HNC [31]. Meta-analysis comparing several prophylactic treatments of RT-induced OM for patients with HNC receiving RT, concluded that PBMT associated with oral care may be more effective than standard oral care alone [32]. Our study confirms the importance of this combined therapy, expressed by the predominance of OM grade 2, no occurrence of OM grade 4, and no detrimental effects of quality of life throughout the RT.

It was also observed that, although the participants had pain and dysphagia/odynophagia, the mean intensity of these symptoms remained below 50%. Dysgeusia and xerostomia were common events; however, the intensity of symptoms (pain, dysphagia, and odynophagia) maintained stable throughout the course of RT. Previous studies reported reduced pain [14, 30], decreased xerostomia [14, 19, 33], improved dysphagia [18], and a reduced need for parenteral nutrition [34]. Although our study did not observe a positive effect on dysgeusia, another study in patients with burning mouth syndrome demonstrated improvements in both burning and taste [35].

In the present study, POCP/PBMT was administered for 5 days per week as recommended by other clinical trials [14, 16–18, 36–38]. Results demonstrate that there was an impairment in quality of life (OHIP-14), but the scores remained stable from the 7th RT session, and this can be explained by the improvement in the control of oral complications. PROMS score also confirmed that the impact on the quality of life was discrete and stable from the 14th RT session.

There is scarce data on the impact of POCP and concomitant daily PBMT on patient quality of life. Studies reported the positive effects on quality of life due to the use of PBMT in patients with HNC under RT adjuvant [16, 17, 38], although none of these studies associated POCP to the patient preventive care. Gautam et al. [17] compared the effects of PBMT and placebo on patient quality of life and reported positive effects in both groups, although results were substantially better in the PBMT group, possibly due to the decrease in the duration of OM and incidence of and severity of xerostomia.

Interruption of RT due to adverse effects of OM and systemic complications has been a major challenge for the treatment of HCN patients. A study by Vera-Llonch et al. [1] found that 84% of the patients undergoing RT in the head and neck region interrupted the RT due to severe OM and showed that the higher was the severity of the OM, the longer was the duration of RT interruption. In our study, only 5% of the participants interrupted their RT due to OM. Nevertheless, the highest interruption rate was due to technical maintenance of the RT equipment, corresponding to 46.7% of all RT interruption events. Similar results were reported by another study [3] that found that among the main causes of RT interruption were calendar holidays and maintenance of the RT apparatus. In our study, only 3 participants out of 61 discontinued RT treatment due to OM, which suggests that PBMT combined with and rigorous POCP were effective in reducing the incidence and duration of RT interruption.

All participants had advanced tumors (T3-T4) with a predominance of the oropharyngeal site (50%), with lymph node metastasis greater than 2 cm (50%), histological grade 2 or 3 (92.8%), and performed only RT and CT concomitantly (64.3%). However, when disease-free and overall survival were analyzed, regardless of clinical-pathological factors, oral adverse effects, number of interruptions, and period of discontinuation of RT had no significant association. These results indicated that the disease-free survival rate and overall survival were only lower for participants who did not respond favorably to RT treatment. Deceased participants had advanced tumors with histological grade of malignancy between 2 and 3, and most of them had locoregional metastasis. It is well-known that nodal involvement is generally indicative of advanced tumors, worse prognosis, and lower disease-free and overall survival rates [39]. In addition, tumors with a histological grade of moderate or undifferentiated malignancy are associated with advanced neoplasms [40], higher risk of local recurrence and regional metastasis [41], and worse survival rates [40].

From all eligible participants in this study, only 61 agreed to be monitored daily by the dental team. Non-adherence may be associated with factors inherent to the disease itself, especially in advanced stages, and poor socioeconomic conditions, which are frequently associated with limited cognitive ability and lack of family or caregiver support. Patient adherence to the POCP was one of the main difficulties in the study. However, to

obtain favorable results, strict patient control and uninterrupted monitoring are essential for a successful outcome, which may not be possible in all clinical settings.

Findings from this study may be interpreted within the context of the performance status of the patient and the clinical stadium of the tumor, as well as the individual assessment of the potential contribution of these interventions for the patient overall clinical status and quality of life. It would be also useful to estimate the minimum change in the outcome of interest that the patients would perceive as important, either beneficial or harmful, and that would lead the patient or clinician to consider a change in management of the patient condition. Nevertheless, it is a difficult task to use a single approach for determining the minimally important differences in outcomes, due to the POCP and PBMT protocols, which will depend on the characteristics of the population studied and the severity of the problem in a group of head and neck cancer patients [42]. Therefore, the statistical significance of changes in patient outcomes (quality of life, plaque index, and periodontal scores) should be considered with caution, since the clinical significance of these changes is uncertain. The favorable outcomes observed in our study may be highly influenced by the strict protocol of daily monitoring and maintenance of the patients' oral condition by the dental care team, which may not be the routine protocol for regular patients undergoing radiochemotherapy in a real clinical setting.

Conclusion

Within the limitations of this observational cohort study, findings of this study suggest a positive influence of the dental team in the management of oral preventive care for the HNC patient submitted to RT. The PBMT associated with a rigorous and well-controlled POCP resulted in satisfactory control of oral adverse effects, reduction of quality of life impacts, and interruption of RT regimen due to severe OM. However, a study with a randomized controlled trial design is needed to confirm the effectiveness of the POCP.

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Compliance with ethical standards

This prospective observational study was conducted in the Araujo Jorge Hospital (Association of Combat Cancer in Goias), in Goiania, Brazil, and was approved by the local research ethics committee (approval no. 012/12).

Conflict of interest The authors declare that they have no conflict of interest.

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