

The Impact of Photobiomodulation for Oral Mucositis on the Quality of Life of Head and Neck Cancer patients undergoing Radio Chemotherapy

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Abstract

Background: Photobiomodulation (PBM) has been used to prevent and manage Oral Mucositis (OM) due to its bio stimulating properties. We evaluated the impact of PBM for OM on the Quality of Life (QOL) of Head and Neck (HNC) patients undergoing radio-chemotherapy.

Methods: Patients were allocated randomly to the Laser (LO) and Control Group (LS). PBM was used three times a week. QoL assessment were undertaken at the 1st, 6th, 12th, 18th, and 24th radiotherapy sessions.

Results: The overall QOL scores decreased in both groups. A comparative analysis between the LO and LS groups demonstrated a worsening over time in the saliva, taste, swallowing, and recreation domains ($p < 0.05$). The LS group demonstrated a greater impairment of QOL in chewing at the 1st ($p = 0.011$), 18th ($p = 0.023$) and 24th sessions ($p = 0.012$).

Conclusion: PBM prevented the manifestation of more severe OM degrees, improving the QOL at oral related domains.

Keywords: Low Level Laser Therapy • Oral mucositis; Head and neck cancer • Radiotherapy • Quality of Life

Introduction

The World Health Organization (WHO) defines quality of life (QOL) as an individuals' perception of their position in life in the context of the culture and value in which they live and in relation to their goals, expectations, standards, and concerns. Questionnaires that assess the QOL are being increasingly proposed for cancer patients [1]. Several studies mention the importance of these instruments outcomes for an adequate cancer treatment and the establishment of coping strategies since patients diagnosed with cancer have negative psychological outcomes that initiate right after the diagnosis and continue after treatment [2].

Head and neck cancer (HNC) comprises malignant tumors arising from the upper aerodigestive tract, extending from the surface of the lips to the esophagus, and includes any anatomical structure in this region. By 2025 it is estimated over 21 million new cases of cancer worldwide, of which 1 million are HNC. Among the established risk factors are the use of tobacco and the ingestion of alcohol, and their combined use has multiplicative effects on the risk of tumor development [3].

Amidst all the acute complications that can affect patients undergoing HNC treatment, oral mucositis (OM) is the most common. OM is an inflammatory mucosal condition that is clinically characterized by ulceration, edema, pain, erythema, and

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hemorrhage. Additionally, OM can increase the risk for local and systemic infections, compromises nutritional intake and may require unplanned treatment interruptions. It also can increase treatment costs and affect the patients' QOL.

Currently, the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) recommends PBM for OM prevention in patients diagnosed with HNC. Several studies have elucidated the effectiveness of PBM in preventing and managing OM as well as its impacts on the QOL of patients undergoing cancer treatment. The adverse effects caused by OM on the individuals' QOL are not only restricted to pain and physical limitations, but they also include social and psychological aspects, such as social isolation, depression, and impairment of future perceptions. However, given the different protocols for PBM, it is difficult to compare and discuss the data between studies [4].

Despite the various complications that OM can trigger and that PBM is a non-pharmacological, minimally invasive and a simple technique, in addition to being recommended for the prevention of OM in patients undergoing cancer treatment, the present study aimed to evaluate the impact of PBM on the QOL of HNC patients undergoing radio-chemotherapy treatment [5].

Material and Methods

This was a quantitative and prospective study. This study's ethics approval was obtained from the Hospital Santo Antônio/Irmã Dulce Social Works (OSID) National Human Research Ethics Committee (CAAE: 46909315.1.3001.553). All participants gave written informed consent after information about the proposed study and primary objectives.

A total of 27 patients diagnosed with HNC, undergoing exclusive radiotherapy or concomitant radio-chemotherapy from December 2016 to April 2018 at the High Complexity in Oncology Unit (UNACON) Nossa Senhora de Fátima, of the Irmã Dulce Social Works from the Unified Public Health System (SUS) were enrolled in this study.

Patients over the age of 18; diagnosed with malignant neoplasms in the head and neck region undergoing exclusive radiotherapy and/or concomitant radio-chemotherapy treatment; who had not initiated cancer treatment; and those with at least 24 sessions of the radiotherapy protocol were included in the study. Patients who underwent exclusive surgical treatment; those who did not participate in any of the interview sessions and individuals with any systemic disease and / or autoimmune diseases that could impair tissue repair in the oral cavity were excluded.

Medical information such as cancer diagnosis, tumor staging, treatment protocol, treatment side-effects, and length of treatment side-effects were extracted from the patients' medical charts. To characterize the sample's socio-demographic characteristics, a questionnaire that retrieved data including age, gender, education level, monthly family income, smoking habits or alcohol consumption was applied at the first appointment, before the commencement of the treatment protocol.

Patients were randomly allocated to two groups: intervention group - Laser On (LO) and control group - Laser Sham (LS), based on the medical record registration number. For the LO group, a low-power

Aluminum Gallium Arsenide (AlGaAs) PBM device, Twin Flex® (MM Optics, São Carlos, Brazil), with a maximum output power of 86.7 mW, active tip area of 0.1256 cm², and continuous wavelength of 660 nm, was applied to specific oral cavity points, three times a week, on alternate days. The dosimetry used in each application was 2 J/cm², 0.3 J per point, for 3 seconds. A total of 28 equidistant laser application points were outlined, never delivered over an active tumor site, with a safety margin of at least 5 cm. PBM was applied to the lips mucosae (three points each lip), left and right buccal mucosae (three points each), hard and soft palate (three points each), the anterior floor of the mouth (one point), lateral borders of the tongue (three points on each side) and dorsal surface of the tongue (six points). The LS group (control) underwent the same treatment protocol as the LO group, but light irradiation was deactivated. The patient evaluation was performed at the 1st, 6th, 12th, 18th and 24th radiotherapy sessions and included full intraoral examinations aimed at assessing soft tissue changes, mainly OM, according to the WHO scale.

The QOL was assessed at the same patient evaluation period (1st, 6th, 12th, 18th and 24th radiotherapy treatment sessions), using a Brazilian Portuguese validated version (Department of Head and Neck Surgery and Otorhinolaryngology at the Hospital de Câncer AC Camargo-SP, 2004) of the University of Washington Quality of Life Questionnaire (UW-QOL). The UW-QOL consists of 12-items that assess 12 QOL domains: pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood, and anxiety. Each of the domain-specific items is scored from 0 to 100, and the lower the score, the lower the QOL per domain.

A descriptive analysis was performed for the socio-demographic characteristics of the sample, tumor staging, and treatment side-effects. The software R (version 3.6.1) was used for the descriptive (median and quartiles) database analyses. The distribution of data was tested for normality using the Shapiro-Wilk normality test.

To identify significant differences among the QOL domains and PBM therapy or control and the severity of OM, the non-parametric Mann-Whitney U test was used. To evaluate the differences among the QOL domains, PBM protocol, and OM, among the evaluation periods, the Friedman's test was used, followed by the posthoc Dunn's test. The significance level was set at 5%. To verify individuals' quality of life, according to laser groups and evaluation time, the non-parametric Student's t test was used. The analysis was performed using Prisma GraphPad (version 7.0, United States) and a significance level of 5% was established.

Results

A total of 27 patients, ages ranged between 24 and 75 years, were enrolled in this study, of which 18 were allocated to the LO group and 9 to the LS group. The majority of participants were male (77.8%), the most prevailing monthly income was of up to 1 minimum wage (51.9%), and a significant fraction of users had incomplete lower secondary education (55.6%). The socio-demographic characteristics of the patients are summarized in Table 1.

Variables	N	%
Gender		
Male	21	77.8
Female	6	22.2
Marital status		
Single	7	25.9
Married	13	48.1
Widowed	1	3.7
Separated/ divorced	3	11.1
Other	3	11.1
Average household monthly income*		
No income	6	22.2
Up to 1 minimum wage	14	51.9
From 1 to 2 minimum wages	6	22.2

**National minimum wage equals to 1045 BRL/Month in Brazil (approximately 200 USD - 2020 values).

Table 1 : Socio-demographic characteristics.

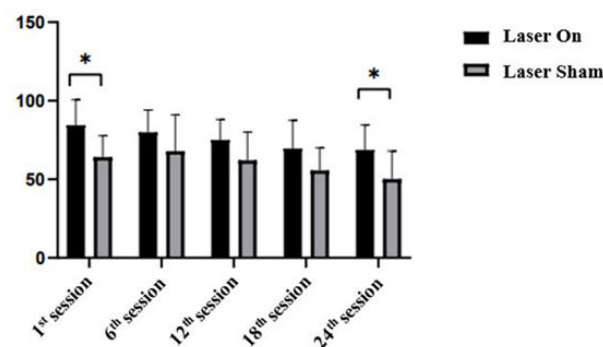
Evaluation of patients' clinical, pathological, and lifestyle characteristics demonstrated that in both groups, patients were predominantly alcoholics and smokers, and the larynx was the most frequent primary site of diagnosis (37%). Most patients had advanced stage III/IV (77.7%) disease and grades I and II OM (40.7%). Table 2 shows the absolute and relative frequency of each group and the total study population variables.

Variables	Laser On (n=18)	Laser (n=9)	Sham	Total (n=27)
Drink alcohol	n/%	n/%		n/%
Yes	11 (61.1%)	4 (44.4%)		15 (55.5%)
No	7 (38.8%)	5 (55.5%)		12 (44.4%)
Smoker				
Yes	12 (66.6%)	6 (66.6%)		18 (66.6%)
No	6 (33.3%)	3 (33.3%)		9 (33.3%)
Primary site (Cancer diagnosis)				
Oropharynx	6 (33.3%)	3 (33.3%)		9 (33.3%)
Larynx	9 (50%)	1 (11.1%)		10 (37%)
Left eye	1 (5.5%)	-		1 (3.7%)
Oral cavity	2 (11.1%)	3 (33.3%)		5 (18.5%)
Hypopharynx	-	2 (22.2%)		2 (7.4%)
Stage				
Stage II	5 (27.7%)	1 (11.1%)		6 (22.2%)
Stage III and IV	13 (72.2%)	8 (88.8%)		21 (77.7%)
Mucositis grade				
Grade 0	6 (33.3%)	2 (22.2%)		8 (29.6%)

Grade I and II	7 (38.8%)	4 (44.4%)	11 (40.7%)
Grade III and IV	5 (27.7%)	3 (33.3%)	8 (29.6%)

Table 2 : Patients' clinical, pathological and lifestyle characteristics.

An overall decrease in the UW-QOL scores was observed in both LO and LS groups throughout radiotherapy. A comparison between the study groups showed that patients in the LS group had a significantly lower QOL in both 1st and 24th radiotherapy sessions, when compared to LO groups, as shown in Figure 1.



* Indicate a significant difference in the time groups.

Figure 1 : Both groups presented an overall decrease in the UW-QOL scores. LS group presented a significantly lower QOL in both 1st and 24th radiotherapy sessions, when compared to LO groups. *P=0.005.

Tables 3, 4, 5 and 6 present the QOL domains evaluated at each radiotherapy session and over time assessed by the UW-QOL questionnaire, among the PBM groups and the clinically observed OM degrees. A statistically significant worsening of the individuals' QOL was observed in the OM groups, over time, in the following domains: saliva (OM grade 0: $p<0.001$; OM grades I and II: $p=0.002$ and OM grades III e IV: $p=0.005$), taste (OM grade 0: $p=0.030$; OM grades I and II: $p<0.001$; OM grades III and IV: $p=0.009$), swallowing (OM grade 0: $p=0.025$; OM grades I and II: $p=0.009$; OM grades III and IV: $p=0.039$) and speech (OM grade 0: $p=0.046$). Saliva was the only domain where it was possible to identify which were the radiotherapy sessions that provided a significant statistical difference: between the 1st and 24th radiotherapy session in the OM grade 0 and OM grades I and II groups and between the 1st and the 18th session in the OM grades III and IV group. Overall, it was observed that some domains presented with statistically significant results in specific sessions. The chewing domain showed a significant score reduction in the OM grades III and IV group in the 12th session ($p = 0.039$). This same group showed significant impairment in the anxiety domain at the 18th radiotherapy session ($p = 0.048$). For the pain domain, the most affected individuals were those with OM grades I and II in the 6th session ($p = 0.035$).

QOL	Sessi ons	Laser On	Laser Sham	p- value	OM grade 0	OM grade s	OM grade s	p- value
Domai ns						I and II	III and IV	
Chewing	1st	100.0(100.0-100.0)	50.0(0.0-75.0)	0.011	100.0(62.5-100)	100.0(0.0-100.0)	75(12.5-100.0)	0.63
	6th	100.0(87.5-100.0)	50.0(0.0-100.0)	0.16	100.0(100.0-100.0)	100.0(0.0-100.0)	75(12.5-100.0)	0.254
	12th	100.0(50.0-100.0)	100.0(0.0-100.0)	0.495	100.0(62.5-100)	100.0(100.0-100.0)	50.0(0.0-87.5)	0.039
	18th	100.0(50.0-100.0)	0.0(0.0-75.0)	0.023	100.0(62.5-100)	100.0(0.0-100.0)	0.0(0.0-87.5)	0.091
	24th	100.0(50.0-100.0)	0.0(0.0-75.0)	0.012	100.0(62.5-100)	100.0(0.0-100.0)	50.0(12.5-87.5)	0.246
p-value		0.252	0.278		0.8	0.369	0.347	
Saliva	1st	100.0(100.0-100.0)A	100.0(83.5-100.0)	0.781	100.0(75.3-100.0)A	100.0(100.0-100.0)A	100.0(100.0-100.0)A	0.83
	6th	67.0(67.0-100.0)	67.0(67.0-100.0)	0.743	100.0(67.0-100.0)	67.0(30.0-100.0)	67.0(67.0-100.0)	0.183
	12th	67.0(30.0-100.0)	67.0(30.0-83.5)	0.433	67.0(41.5-100.0)	67.0(30.0-100.0)	67.0(30.0-67.0)	0.565
	18th	67.0(30.0-75.3)B	33.0(30.0-67.0)	0.118	67.0(41.5-91.8)	67.0(30.0-67.0)	33.0(30.0-67.0)B	0.366
	24th	33.0(30.0-67.0)B	67.0(30.0-67.0)	0.631	33.0(30.0-67.0)B	33.0(0.0-67.0)B	67.0(30.0-67.0)	0.648
p-value		<0.001	0.005*		<0.001	0.002	0.005	
Taste	1st	100.0(100.0-100.0)A	100.0(16.5-100.0)	0.176	100.0(75.3-100.0)	100.0(33.0-100.0)	100.0(49.8-100.0)	0.951
	6th	100.0(33.0-100.0)	75.0(0.0-100.0)	0.348	87.5(41.5-100.0)	100.0(0.0-100.0)	100.0(33.0-100.0)	0.821
	12th	67.0(30.0-100.0)	33.0(0.0-66.5)	0.106	33.5(0.0-100.0)	33.0(30.0-100.0)	67.0(30.0-100.0)	0.692
	18th	33.0(0.0-41.5)B	0.0(0.0-33.0)	0.232	33.0(0.0-58.5)	0.0(0.0-33.0)	16.5(0.0-33.0)	0.512
	24th	16.5(0.0-100.0)	0.0(0.0-0.0)	0.076	16.5(0.0-91.8)	0.0(0.0-0.0)	16.5(0.0-83.3)	0.263
p-value		<0.001	0.003*		0.03	<0.001	0.009	

Table3: Score analysis of the Chewing, Saliva and Taste domains of the UW-QOL Questionnaire between the laser and OM groups during the study periods and overtime.

QOL	Sessi ons	Laser On	Laser Sham	p- value	OM grade 0	OM grade s	OM grade s	p- value
Domai ns						I and II	III and IV	
Swallowing	1s	100.0(91.8-100.0)	67.0(30.0-100.0)	0.053	100.0(75.3-100.0)	100.0(33.0-100.0)	67.0(41.5-100.0)	0.362
	6th	100.0(67.0-100.0)	33.0(30.0-100.0)	0.041	100.0(100.0-100.0)	67.0(30.0-100.0)	67.0(30.0-100.0)	0.082

	12th	67.0(30.0-100.0)	67.0(30.0-100.0)	0.9	67.0(41.5-100.0)	67.0(30.0-100.0)	33.0(30.0-67.0)	0.33
	18th	67.0(30.0-100.0)	33.0(0.0-67.0)	0.053	67.0(30.0-100.0)	67.0(30.0-100.0)	33.0(30.0-83.3)	0.626
	24th	67.0(30.0-100.0)	33.0(0.0-50.0)	0.053	83.5(30.0-100.0)	33.0(30.0-100.0)	33.0(30.0-58.5)	0.302
p-value		<0.001**	0.001*		0.025	0.009	0.039	
Activity	1st	75.0(50.0-100.0)	75.0(50.0-87.5)	0.433	87.5(50.0-100.0)	50.0(50.0-100.0)	75.0(50.0-100.0)	0.34
	6th	75.0(50.0-100.0)	75.0(30.0-100.0)	0.705	75.0(50.0-100.0)	75.0(50.0-100.0)	87.5(30.0-100.0)	0.459
	12th	75.0(50.0-100.0)	50.0(30.0-75.0)	0.059	75.0(50.0-93.8)	75.0(50.0-100.0)	50.0(50.0-93.8)	0.405
	18th	62.5(50.0-100.0)	75.0(50.0-87.5)	0.94	75.0(50.0-93.8)	75.0(50.0-100.0)	50.0(30.0-93.8)	0.637
	24th	62.5(50.0-81.3)	50.0(20.0-62.5)	0.118	62.5(50.0-93.8)	50.0(20.0-75.0)	50.0(50.0-75.0)	0.559
p-value		0.098	0.298		0.126	0.608	0.701	
Recreation	1st	100.0(68.8-100.0)	50.0(20.0-75.0)	0.017	75.0(50.0-100.0)	50.0(20.0-100.0)	87.5(50.0-100.0)	0.36
	6th	75.0(50.0-100.0)	50.0(30.0-100.0)	0.375	75.0(50.0-100.0)	75.0(50.0-100.0)	62.5(50.0-100.0)	0.654
	12th	75.0(50.0-100.0)	75.0(30.0-87.5)	0.463	75.0(50.0-100.0)	75.0(50.0-100.0)	75.0(50.0-93.8)	0.826
	18th	50.0(40.0-100.0)	50.0(50.0-100.0)	0.495	87.5(50.0-100.0)	50.0(50.0-100.0)	50.0(30.0-100.0)	0.601
	24th	62.5(40.0-100.0)	50.0(20.0-87.5)	0.433	87.5(30.0-100.0)	50.0(20.0-100.0)	50.0(30.0-68.8)	0.504
p-value		0.006*	0.206		0.941	0.927	0.145	

Table 4: Score analysis of the Swallow, Activity and Recreation domains of the UW-QOL Questionnaire between the laser and OM groups during the study periods and overtime.

QOL	Sessi ons	Laser On	Laser Sham	p- value	OM grade 0	OM grade s	OM grade s	p- value
Domai ns						I and II	III and IV	
Appearance	1st	100.0(75.0-100.0)	75.0(50.0-87.5)	0.059	100.0(75.0-100.0)	75.0(50.0-100.0)	87.5(50.0-100.0)	0.373
	6th	87.5(75.0-100.0)	75.0(62.5-100.0)	0.668	75.0(75.0-100.0)	100.0(75.0-100.0)	87.5(75.0-100.0)	0.885
	12th	100.0(75.0-100.0)	75.0(50.0-87.5)	0.145	100.0(75.0-100.0)	100.0(75.0-100.0)	75.0(50.0-100.0)	0.8
	18th	100.0(50.0-100.0)	75.0(30.0-87.5)	0.253	100.0(56.3-100.0)	75.0(50.0-100.0)	62.5(20.0-93.8)	0.185
	24th	75.0(50.0-100.0)	75.0(62.5-87.5)	0.275	87.5(50.0-100.0)	75.0(50.0-100.0)	75.0(50.0-75.0)	0.69

p-value		0.592	0.298		0.357	0.459	0.057	
Shoulder	1st	100.0(67.0-100.0)	67.0(67.0-100.0)	0.403	83.5(67.0-100.0)	100.0(67.0-100.0)	100.0(67.0-100.0)	0.861
	6th	100.0(67.0-100.0)	100.0(50.0-100.0)	0.82	100.0(75.3-100.0)	100.0(67.0-100.0)	100.0(41.5-100.0)	0.718
	12th	100.0(67.0-100.0)	100.0(67.0-100.0)	0.561	100.0(41.5-100.0)	100.0(67.0-100.0)	83.5(67.0-100.0)	0.516
	18th	100.0(67.0-100.0)	100.0(67.0-100.0)	0.561	100.0(100.0-100.0)	100.0(67.0-100.0)	100.0(67.0-100.0)	0.298
	24th	100.0(67.0-100.0)	100.0(50.0-100.0)	0.596	100.0(41.5-100.0)	100.0(67.0-100.0)	83.5(67.0-100.0)	0.654
p-value		0.920	0.827		0.266	0.722	0.612	
Speech	1st	100.0(67.0-100.0)	67.0(30.0-83.5)	0.106	67.0(15.0-100.0)	67.0(30.0-100.0)	100.0(67.0-100.0)	0.3
	6th	67.0(67.0-100.0)	100.0(33.0-100.0)	1	100.0(41.5-100.0)	67.0(30.0-100.0)	67.0(67.0-100.0)	0.832
	12th	83.5(8.5-100.0)	67.0(16.5-67.0)	0.106	67.0(15.0-91.8)	67.0(30.0-100.0)	67.0(15.0-100.0)	0.847
	18th	67.0(67.0-100.0)	67.0(30.0-67.0)	0.118	67.0(15.0-91.8)	67.0(30.0-100.0)	67.0(67.0-100.0)	0.318
	24th	67.0(30.0-100.0)	67.0(30.0-67.0)	0.131	50.0(8.3-91.8)	67.0(30.0-100.0)	67.0(67.0-91.8)	0.579
p-value		0.094	0.11		0.046	0.485	0.124	

Table 5: Score analysis of the Appearance, Shoulder and Speech domains of the UW-QOL Questionnaire between the laser and OM groups during the study periods and overtime.

QOL	Sessions	Laser On	Laser Sham	p-value	OM grade 0	OM grade I and II	OM grade III and IV	p-value
Domain								
Pain	1st	100.0(68.8-100.0)	50.0(50.0-75.0)	0.059	100.0(62.5-100.0)	75.0(50.0-100.0)	75.0(50.0-100.0)	0.423
	6th	87.5(50.0-100.0)	75.0(50.0-100.0)	0.348	100.0(81.3-100.0)	50.0(50.0-75.0)	87.5(50.0-100.0)	0.035
	12th	62.5(50.0-100.0)	75.0(25.0-75.0)	0.631	75.0(50.0-100.0)	75.0(50.0-75.0)	75.0(50.0-93.8)	0.644
	18th	75.0(50.0-100.0)	50.0(50.0-75.0)	0.145	75.0(63.0-100.0)	50.0(50.0-100.0)	50.0(50.0-68.8)	0.162
	24th	100.0(50.0-100.0)	50.0(37.5-87.5)	0.046	100.0(50.0-100.0)	100.0(50.0-100.0)	50.0(50.0-100.0)	0.545
p-value		0.252	0.278		0.567	0.659	0.605	
Anxiety	1st	67.0(67.0-100.0)	33.0(16.5-83.5)	0.053	67.0(15.0-67.0)	100.0(67.0-100.0)	67.0(30.0-100.0)	0.237

	6th	100.0(67.0-100.0)	67.0(0.0-100.0)	0.403	67.0(67.0-100.0)	100.0(67.0-100.0)	67.0(0.0-100.0)	0.265
	12th	100.0(67.0-100.0)	67.0(30.0-100.0)	0.275	100.0(75.3-100.0)	100.0(67.0-100.0)	67.0(30.0-100.0)	0.344
	18th	100.0(67.0-100.0)	67.0(50.0-100.0)	0.348	67.0(67.0-100.0)	100.0(67.0-100.0)	67.0(30.0-91.8)	0.048
	24th	83.5(30.0-100.0)	67.0(30.0-100.0)	0.561	100.0(41.5-100.0)	100.0(33.0-100.0)	67.0(30.0-67.0)	0.366
p-value		0.783	0.268		0.181	0.283	0.993	
Mood	1st	87.5(8.8-100.0)	100.0(50.0-100.0)	0.94	100.0(56.3-100.0)	100.0(25.0-100.0)	75.0(50.0-100.0)	0.869
	6th	100.0(75.0-100.0)	75.0(50.0-100.0)	0.561	100.0(75.0-100.0)	75.0(50.0-100.0)	100.0(56.3-100.0)	0.291
	12th	100.0(75.0-100.0)	50.0(50.0-100.0)	0.145	100.0(81.3-100.0)	75.0(50.0-100.0)	87.5(50.0-100.0)	0.355
	18th	75.0(50.0-100.0)	75.0(25.0-75.0)	0.561	87.5(63.0-100.0)	75.0(50.0-75.0)	75.0(13.0-93.8)	0.487
	24th	75.0(8.8-100.0)	75.0(37.5-87.5)	0.275	100.0(56.3-100.0)	75.0(25.0-75.0)	75.0(50.0-100.0)	0.089
p-value		0.633	0.849		0.639	0.711	0.545	

Table 6 : Score analysis of the Pain, Anxiety and Mood domains of the UW-QOL Questionnaire between the laser and OM groups during the study periods and overtime.

When evaluating the performance of PBM on the QOL domains, it was observed a statistically significant difference that worsened over time in the saliva (LO: $p < 0.001$ and LS: $p = 0.005$) and taste (LO: $p < 0.001$ and LS: $p = 0.003$) domains, in both groups. In the LO group, the differences in these domains occurred between the 1st and the 18th and between the 1st and the 24th sessions, respectively ($p < 0.001$). It was not possible to identify the exact sessions in the LS group in which the differences occurred. The swallowing domain also showed statistically significant results in both groups (LO: $p < 0.001$ and LS: $p = 0.001$); however, it was not possible to identify the exact session in which this difference occurred. As for the recreation domain, a statistically worsening significant difference was observed only in the LO group ($p = 0.006$), with no specific radiotherapy session. It was also observed a worsening statistically significant difference in some domains at some specific periods when comparing the LO and LS groups. The LS group had a higher compromise on the QOL in the chewing domains in the 1st session ($p = 0.011$), 18th session ($p = 0.023$) and 24th session ($p = 0.012$), swallowing in the 6th session ($p = 0.041$), recreation in the 1st session ($p = 0.17$) and pain in the 24th session ($p = 0.046$).

Discussion

Several factors, including disease severity, tumor site location, and socioeconomic status, can affect both the QOL and the functionality of patients diagnosed with malignant tumors. Literature shows that individuals with lower socioeconomic status and that drink larger amounts of alcohol and smoke more cigarettes are at greater risk for

HNC development, mainly located in the oral cavity, larynx, and pharynx, and are also subjected to a late-stage diagnosis. In the present study, the majority (51.9%) of participants had the larynx as the most frequent site of diagnosis, a monthly income of up to 1 minimum wage, and smoking and drinking habits. Advanced stages of the disease (stages III and IV) are usually associated with a more invasive treatment approach, causing several negative effects such as facial disfigurement and difficulties in speech, chewing, and swallowing.

OM is one of the most debilitating side-effects of cancer therapy in HNC patients and causes many complications, including difficulty in speaking, severe pain, and weight loss²⁰. In contrast, data from this study demonstrated that only grade 0 OM individuals, according to the WHO scale, had speech difficulties^[4].

In agreement with our findings that demonstrated that patients most affected by the pain domain were those not submitted to PBM and those with OM grades I and II, a study observed a decrease in patient-reported soreness of the mouth and throat associated with OM in the PBM group, and thus, oral functions such as eating, swallowing and speaking were greater in the PBM group than those seen in the placebo group. Patients with OM also have a higher dependence on liquid or soft foods, which may lead to psychological impairments⁶, mainly associated with social behavior or eating in public. In the present study, patients diagnosed with higher degrees of OM and those who were not submitted to PBM had greater difficulty in chewing (Table 3). Although the PBM therapy did not prevent OM in all patients, it was noticeable that the group submitted to PBM had a higher percentage of individuals without OM compared to the sham laser group [1-3].

Decreased salivary flow can be observed from the first week of radiotherapy treatment and becomes more evident over time³⁰. A study demonstrated the maintenance of the salivary flow rate after 30 days of the last treatment session in patients that were submitted to PBM when compared to a control group. Saliva acts as a protective barrier and is a lubrication fluid and a flow reduction might contribute to intraoral tissues becoming friable and susceptible to inflammation. Thus, saliva changes possibly contributed to the onset of OM in this cohort of patients and justify the statistically significant values found for this domain. Although our PBM protocol only included oral mucosae sites, the minor salivary glands' intraoral anatomical location allows them to be included within the PBM protocol.

Some adverse effects common in patients with HNC, including xerostomia, dysgeusia and, pain, are directly related to a reduction in the swallowing capacity. Kubrak et al. (2013) reported that an association of OM, xerostomia and dysphagia, causes a reduction in food intake, resulting in weight loss, thus negatively impacting QOL. In addition to these factors, a study demonstrated that patients diagnosed with HNC are prone to have difficulty in swallowing than patients diagnosed with other cancer subtypes. Results from the present study showed that, over time, patients from both groups, regardless of PBM, and all OM grades, presented with difficulties in swallowing. Additionally, it was observed that OM lesions started at the 6th radiotherapy session, and the absence of PBM therapy had a negative effect in swallowing, thus demonstrating that although PBM was not able to prevent OM, it prevented the development of more severe grades (Table 4).

The present study demonstrated that the taste domain had a significant statistical difference, regardless of the use of the PBM therapy or not, and the degree of OM, and showed a decrease in food intake due to the progressive dysgeusia during the radiotherapy sessions (Table 3). The impact on the QOL caused by dysgeusia, mainly associated with the individual's nutritional status, is not restricted to the period of cancer treatment. Taste impairment in these individuals is probably a result of the cumulative doses of radiotherapy, altering the histological structure of the taste pores and the thinning of the papilla epithelium and the delivery of flavor molecules to receptor cells, thus affecting gustatory and olfactory cells. The clinical manifestation of OM does not seem to have a direct correlation with dysgeusia, hence individuals without OM also presented with a significant taste loss. As dysgeusia and OM are mutually independent domains, the relationship between them is mainly due to the social and psychological aspects that the distortion in the taste perception can bring, such as the discomfort of eating in public.

The impact on the QOL of HNC patients can also be associated with disorders in the physical, psychological, and social aspects. It was observed in the present study, a score reduction in the recreation domain in individuals undergoing radio-chemotherapy and diagnosed with advanced-stage disease, which is in agreement with literature reports. Activity and recreation were the physical domains most affected by the treatment side-effects, such as xerostomia and dysphagia. This association is suggested by the relationship that leisure activities may have with eating in public, which are hampered due to salivary dysfunction and difficulty in swallowing. A study conducted by Pierre et al. (2014) points out that these clinical manifestations affect patients' QOL even after the end of treatment.

Conclusion

Although the PBM therapy did not prevent the onset of OM and its related side-effects, the severity of OM was reduced in patients who underwent PBM. Although the small sample size limitation, it was possible to observe that HNC patients had a decrease in QOL, mainly associated with the saliva, taste, swallowing, chewing, anxiety, speech and pain domains in the group that did not undergo PBM. Laser PBM has been studied as an effective tool for the prevention, management, and mitigation of these effects; however, the lack of standardized treatment protocols makes it difficult to compare and prove its effectiveness.

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