Lasers in Medical Science (2023) 38:259
https://doi.org/10.1007/s10103-023-03920-0

ORIGINAL ARTICLE

Photobiomodulation therapy in the treatment of radiotherapy-related trismus of the head and neck

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Received: 9 February 2023 / Accepted: 21 October 2023 / Published online: 8 November 2023

Abstract

This study evaluated photobiomodulation therapy (PBMT) for treatment of trismus in patients undergoing radiotherapy for head and neck cancer (HNC). Sixteen patients, 10 men and 6 women, who had a mouth opening < 35 mm and underwent RT were included. The patients were evaluated daily before and after the PBMT application, measuring mouth opening and performing pain scores for the masticatory muscles using the visual analog scale (VAS). We used the infrared laser (~ 808 nm) extraorally, 0.1 W power, 3 J energy, 30 s (107 J/cm^2) per point, applied to temporalis anterior, masseter muscles, and temporomandibular joints (TMJ). An intraoral point was made in the trigonoretromolar region towards the medial pterygoid muscle. The mean mouth opening of the patients increased by more than 7 mm throughout the treatment. The pain scores on the initial days showed an immediate reduction after PBMT on the ipsilateral side in the muscles and TMJ. Throughout PBMT applications, there was a significant reduction in pain scores in all muscles and the TMJ. The radiation dose of all patients was above 40 Gy, which is the threshold dose for the risk of developing trismus. SPSS software was used and adopted a confidence of 95%. The Kolmogorov–Smirnov normality test, Wilcoxon test, and Spearman correlation were performed. PBMT controls muscular pain and reduced mouth opening limitation in HNC during radiotherapy. Further studies are needed to evaluate the preventive capacity of PBMT protocols for RT trismus-related HNC.

Keywords Trismus · Radiotherapy · Head and neck cancer · Low-level light therapy

Introduction

Although surgical resection is the primary modality for treating head and neck tumors, radiotherapy (RT) and/or chemotherapy (QT) have gained great space as adjuvant therapies and even with curative intent in these cancers. In addition, the improvement of technologies and the development of increasingly effective protocols have given significant space to these therapeutic modalities [1, 2].

Patients who undergo RT alone or in conjunction with QT for SCC treatment in the head and neck region have an average dose of 2 Gy per day as standard in the daily scheme. Therefore, we can estimate an average of 30 to 35 fractions for radical treatment [3, 4]. However, the effects of RT negatively impact the quality of life of these patients because besides generating damage to the DNA of neoplastic cells, RT also affects adjacent healthy tissues [5, 6]. Adverse effects include xerostomia, radiation caries, oral mucositis, radiodermatitis, osteoradionecrosis, oral infection, stomatitis, loss of taste, periodontal disease, and short-, medium-, and long-term trismus, which are the most common [2, 7].

Trismus is a limitation of mouth opening < 35 mm, which can compromise the maxillomandibular function [8]. In patients with head tumors and head and neck cancer, the main etiological factors are tumor invasion in the masticatory muscles, surgical resections involving the masticatory muscles, and especially the radiotherapy treatment itself [8].

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Radio-induced trismus develops mainly due to radiation hitting temporalis, masseter, and medial pterygoid muscles. Patients who receive radiation doses above 40 Gy in these structures develop pain, fibrosis of the masticatory muscles, decreased mandibular movements, and temporomandibular dysfunction [8–10]. The incidence of trismus is considerably high in the first 6 months after the beginning of radiotherapy (44.1%) and reduces even in 3 to 10 years after treatment. However, the values are still significantly high (32.6%); therefore, this is the most severe late sequela of radiotherapy treatment [11]. Trismus directly impacts patients' quality of life; it causes facial appearance changes, difficulties opening the mouth, restricts feeding, and compromises breathing and speech [9].

Recently, a clinical case report has begun to bring tenuous evidence of the efficacy of photobiomodulation (PBM) in treating trismus after radiotherapy. Daily application of laser with infrared wavelength almost wholly reversed the limitation of mouth opening, reduced pain in masticatory muscles, and suggested a low-cost protocol for treating radio-induced trismus [12]. PBM induces immediate oxygen influx on target tissues and the respiratory chain resumption, accelerating intracellular adenosine triphosphate (ATP) synthesis [13–15]. This mechanism attributes anti-inflammatory, analgesic, and healing effects, inducing nerve and muscle repair [15–17].

PBM shows us the potential to biostimulate injured muscles during radiotherapy. However, given the low evidence from case reports, clinical trials are needed to validate this therapeutic option. Thus, this study aimed to evaluate the effectiveness of a PBM protocol to treat and reduce the severity of trismus in patients undergoing radiotherapy for head and neck cancer through a single-arm clinical trial.

Materials and methods

Study design and ethical considerations

This study is a single-arm clinical trial, which followed the CONSORT guidelines for clinical trials. Furthermore, all ethical aspects expressed in Resolution No. 466 of 2012 of the National Health Council/Ministry of Health, which brings the Guidelines and Regulatory Standards for research with human subjects, were respected under the CONEP (National Research Ethics Committee) standard (protocol number 5,182,796).

Participants and clinical setting: inclusion, exclusion, and withdrawal criteria

We included patients over 18 years of age with mouth and oropharyngeal cancer stages I, II, III, or IV, with a mouth opening smaller than 35 mm, and who had been indicated for radiotherapy or chemoradiotherapy of the head and neck. Radiotherapy may be indicated for adjuvant, palliative, or curative treatment and may or may not be associated with chemotherapy, immunotherapy, or biological therapies (Fig. 1).

Patients who withdrew from treatment or the study required a change in the therapeutic protocol, developed extreme toxicity, or died were removed from the study. All patients were treated at the radiotherapy outpatient clinic of the Haroldo Juaçaba Hospital, a High Complexity Oncology Care Center (CACON), from August 2021 to December 2021.

Intervention protocol

After signing the informed consent form and agreeing to participate in the study, we collected the clinical-pathological and sociodemographic data. Prior to beginning the PBMT protocol, a visual inspection of the cavity was performed using a photophore (LED Headlight, InovaStock, Florianopolis, Santa Catarina, Brazil). The participants were submitted to evaluations of maximum interincisal opening with the help of a digital pachymeter (Adaskala stainless steel vernier caliper digital caliper 0–150 mm high precision, Adaskala, Guimarei, Portugal), and the visual analog scale (VAS) was used to define pain scores on palpation in the masticatory muscles for pain during mouth opening before and after laser application.

For the treatment protocol, a therapy XT model laser, diode (DMC, São Carlos, São Paulo, Brazil) with 100 mW of continuous wavelength light output power of 660 ± 10 nm (red) and 820 ± 10 nm (infrared) was used, with an area of 0.28 mm^2 (or 0.0028 cm^2), which, during the protocol applications, was kept in light contact with the treated area. Patients were treated during RT on the day they were referred for trismus treatment and followed until the last RT session.

Following the protocol described by Rodriguez et al. [12] using energy density and application points and de Oliveira Melchior et al. [18] using application points to cover all masticatory muscles, the infrared laser (~ 808 nm) was used extra-oral, with 0.1 W power, 3 J energy, 30 s (107 J/cm^2) per point; totaling 270 s of application and 24 J energy per side, the extra-oral points were applied near the region of the temporomandibular joint described by (A) superior, (B) posterior, and (C) anterior to the mandibular condyle, for the application of point (D) patient is prompted to open mouth and laser is applied intra-auricular towards the tragus. To reach the masticatory muscles, application points will be executed: (E) superior, (F) medium, and (G) inferior in the masseter muscle, a point (H) anterior portion of the temporalis muscle.

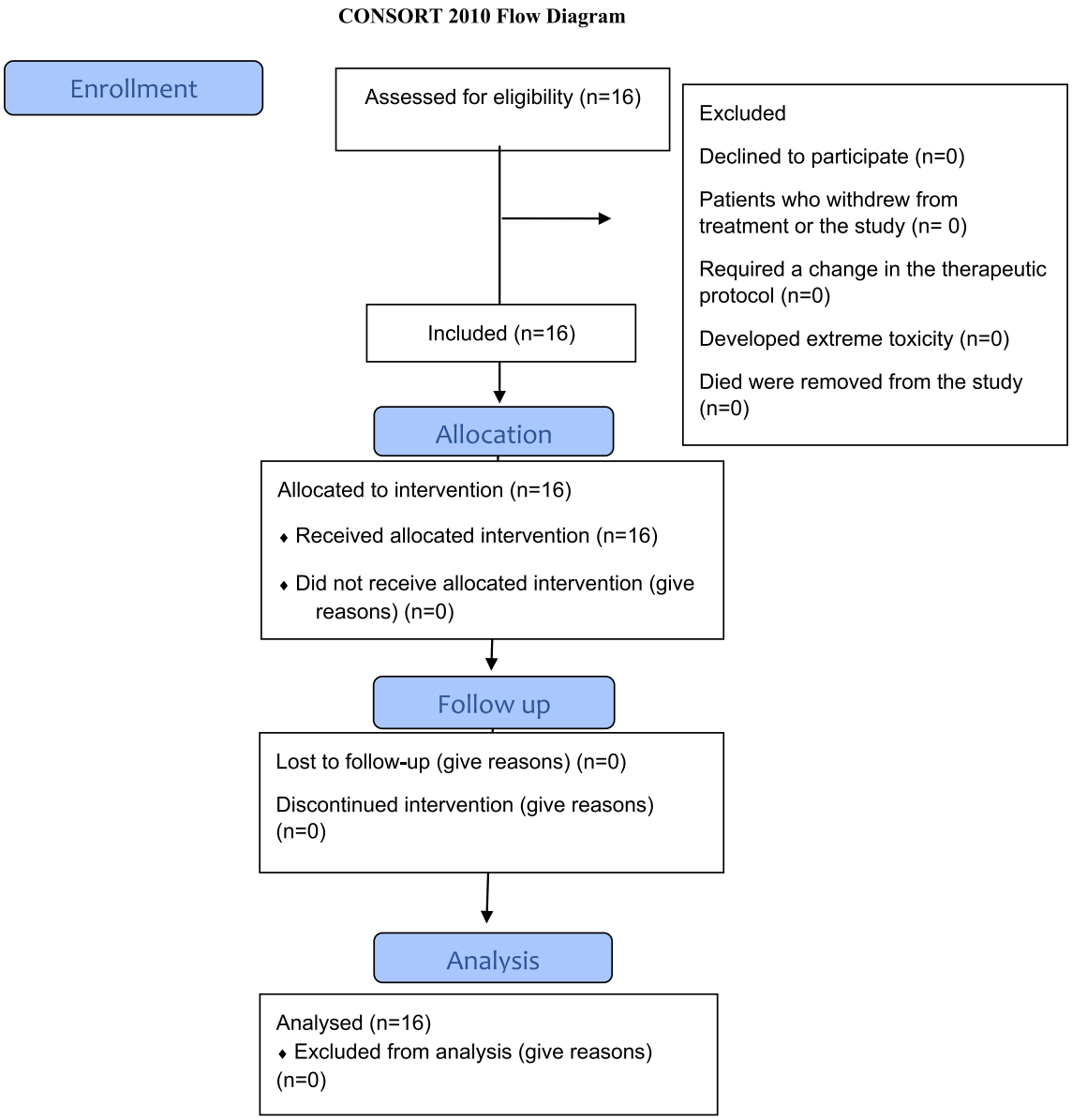

Fig. 1 CONSORT 2010 flow diagram adapted from single-arm clinical trial

We made an intraoral point (I) to reach the medial pterygoid muscle, also using the infrared laser (~ 808 nm), 0.1 W power, 3 J energy, 30 s (107 J/cm^2) per point; totaling 30 s of application, and 3 J energy per side. In patients who had tumor involvement in the masticatory muscle, the laser was performed only on the contralateral side of the lesion (Fig. 2).

Evaluation of trismus and pain in the masticatory muscles

As described by da Silva Neto Trajano et al. [17], in dentate patients, we evaluated the distance between the upper and lower central incisors daily, after entering the study, in millimeters using a pachymeter; in edentulous patients, we measured this distance between the upper and lower lips to estimate the maximum capacity to open the mouth. The patients were also questioned on the same days about their perception of pain in the masticatory muscles using the visual analog scale (VAS) before and after applying PBMT.

Outcomes and data analysis

We evaluated the electronic patient record (EPR) to collect clinical and pathological data, including age, tumor location, tumor characteristics such as pTNM, chemotherapy concomitantly with RT, which chemotherapy was given, presence

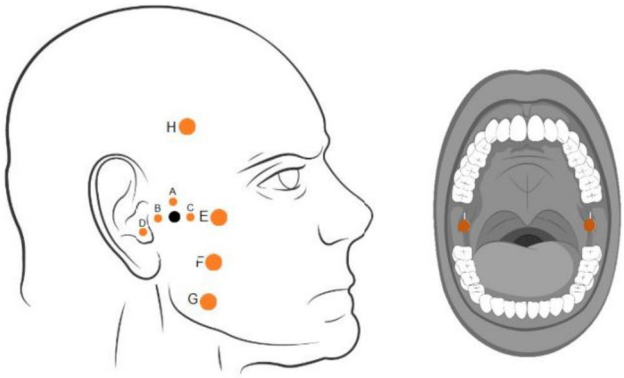

Fig. 2 Schematic design of PBMT's points of application: (**A**) superior, (**B**) posterior, and (**C**) anterior to the mandibular condyle, for the application of point (**D**) the patient will be asked to open the mouth and the laser will be applied intra-auricular towards the tragus. To reach the masticatory muscles, application points will be performed: (**E**) superior, (**F**) medium, and (**G**) inferior in the masseter muscle, a point (**H**) anterior portion of the temporalis muscle. We made an intraoral point (**I**) to reach the medial pterygoid muscle

of a residual lesion, and whether the participant had disease progression during RT.

Design and dose parameters of the temporomandibular joint and masticatory muscles

Based on the radiotherapy treatment, we used CT planning for bilateral delineation of the total dose received in the masseter muscle (MM), medial pterygoid muscle (MPM), temporomandibular joint (TMJ), and lateral pterygoid muscle (LPM). The Varian Healthineers treatment planning system software Eclipse (TPS) (Eclipse™ treatment planning system v18.0, Varian Medical Systems, Jundiaí, São Paulo, Brazil) was used to delimit the total dose to these structures. DVH (dose volume histogram) used to delimitation of these structures was drawn on the planning CT scan in axial sections of 2 mm for every two sections. After delimitation of the anatomical structures, we calculated the minimum, average, and maximum radiation doses received by these structures [19].

Sample calculation

Based on the study by Thor et al. [20], who observed that after head and neck radiotherapy, there is a significant reduction in the mean mouth opening from 49 ± 8 to 39 ± 9 mm, it was estimated necessary to evaluate 16 patients to obtain a sample that represents with 90% power and 95% confidence (*t*-test).

Statistical analysis

The data were tabulated in Microsoft Excel (Office V. 16.0, Portuguese, Brazil) and exported to SPSS software (V 20.0, IBM SPSS, Chicago, USA) in which the analyses were performed adopting a confidence level of 95%. The mouth opening and visual analog pain scale data were submitted to the Kolmogorov–Smirnov normality test, expressed as mean and standard deviation, and compared pre- and immediate post-PBMT periods using the Wilcoxon test (non-parametric data). Additionally, the mean values of each parameter were submitted to correlation analysis with the period of application of therapy and with the dosimetry data by Spearman's correlation.

Sample power

Based on the mean mouth opening gain of the patients treated with PBMT ($+7.19 \pm 4.84$ mm), the sample of 16 patients analyzed has a power of 99% to reject the null hypothesis adopting a 95% confidence and 99.5% adopting a 99% confidence.

Results

Clinical and dosimetry characteristics of patients who developed trismus during head and neck radiotherapy

A total of 16 patients participated in this study, of which the majority were male ($n = 10$) with a mean age of 61.6 ± 13.1 years, ranging from 45 and 82 years. Most of the tumors were located on the tongue ($n = 6$), the most prevalent clinical stage was T4 ($n = 14$) and N0 ($n = 7$) tumors, and no patient was diagnosed with distant metastasis during radiotherapy treatment (Table 1).

The average total radiation dose used in the treatment was 65.4 ± 4.7 Gy ranging from 53 to 70 Gy, and most patients underwent 33 RT sessions ($n = 11$). Only five patients had undergone previous surgery, but 14 underwent chemotherapy (cisplatin = 13/carboplatin = 1). No patient had disease progression during RT, but five patients had the residual disease at the end. On average, patients developed trismus after the 13th RT session, ranging from the 2nd to the 24th session (Table 1).

Only two patients had no tumor area near the masticatory muscles. Nine patients had the involvement of some masticatory muscle on the right side and five on the left side. The areas of muscle invasion by tumor lesions were spared from PBMT. From the diagnosis of trismus on, the patients

Table 1 Clinic characteristics of patients with head and neck radiotherapy-related trismus treated with PBMT

Patient	Sex	Age	Total RT dose (Gy)	Number of fractions	Local of tumor	Stage			Surgery	Cycles of chemotherapy	Disease progression during RT	Residual disease	RT session of start of trismus	MM tumor involvement	Nasogastric tube	Number of PBMT sessions	Mouth opening (mm)		
						T	N	M									Initial	Final	Δ
1	F	65	69	33	Palate	4	0	0	N	5×cisplatin	N	N	7	N	N	26	14.00	23.94	+9.94
2	F	61	66	33	Tongue	4	2	0	Y	7×cisplatin	N	N	24	L	Y	9	21.32	27.62	+6.30
3	M	49	69	33	Tongue	4	1	0	N	6×cisplatin	N	N	9	R	Y	24	0.00	7.47	+7.47
4	F	72	66	33	Tongue	4	0	0	N	7×cisplatin	N	N	5	N	N	28	12.00	28.34	+16.34
5	M	45	69	33	Tongue	4	0	0	N	8×cisplatin	N	Y	9	L	Y	24	0.00	0.00	0.00
6	M	54	68	33	Oropharynx	4	0	0	N	7×cisplatin	N	N	12	R	N	21	29.35	31.43	+2.08
7	M	62	59	33	Inferior lip	4	3	0	Y	7×cisplatin	N	N	14	R	N	19	22.12	35.00	+12.88
8	F	53	70	33	Palate	4	1	0	N	5×cisplatin	N	Y	24	L	N	9	18.44	22.12	+3.68
9	M	55	64	32	Palate	4	2	0	Y	8×cisplatin	N	N	4	R	N	28	22.43	24.40	+1.97
10	F	82	70	33	Palate	2	0	0	N	5×cisplatin	N	N	5	L	N	28	26.42	34.50	+8.08
11	M	78	60	30	Cheek	4	3	0	Y	N	N	N	18	R	N	12	6.64	10.40	+3.76
12	F	81	64	33	Tongue	4	0	0	N	N	N	N	10	R	N	23	16.62	25.00	+8.38
13	M	48	65	30	Cheek	4	3	0	N	4×cisplatin	N	Y	21	R	N	9	16.73	25.08	+8.35
14	M	49	65	25	Tongue	4	1	0	Y	6×cisplatin	N	N	18	L	N	7	10.41	22.08	+11.67
15	M	51	53	22	Oropharynx	4	3	0	N	6×cisplatin	N	Y	12	R	N	10	25.00	38.20	+13.20
16	M	80	69	33	Palate	3	0	0	N	5×carboplatin	N	Y	21	R	N	12	30.00	31.00	+1.00

M, male; *F*, female; *RT*, radiotherapy; *N*, no; *Y*, yes; *R*, right; *L*, left; *MM*, masticatory muscles

The average of mouth opening increase significantly from initial (17.00±9.36 mm) to final (24.16±10.36 mm) of evaluation period ($p<0.001$). The average improvement in mouth opening was +7.19±4.84 mm. Initial and final mouth opening were significantly correlated ($p<0.001$, $r=0.884$), but initial ($p=0.886$) or final ($p=0.095$) mouth opening did not correlate with improvement in mouth opening

underwent PBMT until the end of radiotherapy treatment. The mean number of PBMT applications was 18 ± 8 ranging from 7 to 28 (Table 1).

In dosimetry evaluation showed that ipsilateral medial pterygoid muscle received the maximum radiation minimum dose, radiation average dose ($p < 0.001$), and the second maximum radiation maximum dose ($p < 0.001$). The ipsilateral masseter muscle received the maximum radiation maximum dose; contralateral temporal muscle received the minimum radiation minimum dose and minimum average radiation dose. Contralateral TMJ received the minimum radiation maximum dose.

All contralateral studied structures received lower doses than ipsilateral structures ($p < 0.05$) (Table 2).

PBMT reduces pain and significantly increases mouth opening in irradiated head and neck patients with trismus

The mean initial mouth opening of the patients was 17.00 ± 9.36 mm. After completion of radiotherapy and PBMT sessions, the patients reached a mean of 24.16 ± 10.36 mm, values significantly higher than the initial period ($p < 0.001$). The mean gain in mouth opening was 7.19 ± 4.84 mm, ranging from 1.00 to 16.34 mm. Only one patient showed no improvement in mouth opening (patient 5) (Table 1, Fig. 3).

Men and women did not differ significantly in mouth opening gain ($p = 0.325$). The site of primary tumor involvement ($p = 0.625$), T staging ($p = 0.445$), N ($p = 0.641$), previous surgery ($p = 0.948$) or chemotherapy ($p = 0.739$), and residual remaining disease ($p = 0.293$) also did not significantly influence the primary outcome. Patients with some involvement of the masticatory muscles by tumor tissue had lower mean gain mouth opening (6.34 ± 4.39 mm) than patients without such involvement (13.14 ± 4.52), although there was no statistical difference ($p = 0.060$). Age ($p = 0.812$), total radiation dose ($p = 0.096$), number of PBMT ($p = 0.927$) or RT sessions ($p = 0.151$), RT session in which trismus was diagnosed ($p = 0.437$), initial ($p = 0.886$) or final ($p = 0.095$) mouth opening gain showed no correlation with mouth opening gain (Table 1).

The patients were evaluated for a maximum of 28 radiotherapy sessions, starting with 16 patients and ending with four (Table 3). Immediately after the PBMT application, the mean mouth opening significantly increased in 17 of the 28 periods ($p < 0.05$). As a result, the mean daily gain in mouth opening was + 1.69 ± 2.15 mm. Before PBMT, the mean mouth increased 39% each day ($p < 0.001$, $r^2 = 0.390$), and immediately after PBMT, it showed a significant increase of 31.2% each day over the 28 days ($p = 0.002$, $r^2 = 0.312$) (Table 3).

The mouth opening pain scores significantly reduced in 19 of the 28 periods ($p < 0.05$). The mean daily reduction of pain during mouth opening was − 0.56 ± 1.19 mm, ranging from − 1.25 ± 1.89 to 0.17 ± 0.98 mm. Before PBMT, the mean pain showed a significant reduction of 53.8% each day ($p < 0.001$, $r^2 = 0.538$) and immediately after PBMT showed 37.2% of reduction every day over the 28-day evaluation period ($p = 0.001$, $r^2 = 0.372$) (Table 4).

PBMT reduces masticatory muscle pain in head and neck radiated trismus patients

Regarding pain on palpation in the masticatory muscles, PBMT reduced pain immediately after application on some days in the masseter muscle. In the ipsilateral masseter to the RT beam input immediately after PBMT, there was a reduction in pain scores on palpation on days 5 ($p = 0.026$), 19 ($p = 0.038$), and 20 ($p = 0.041$). The daily reduction of pain scores in ipsilateral masseter was 31.2% ($p = 0.002$) before PBMT and 28.5% ($p = 0.003$) immediately after PBMT over the 28 days of evaluation (Table 3).

In the temporal muscles, there was no reduction in pain scores on palpation on any day of assessment. However, in the ipsilateral temporal, there was a mean daily reduction of 38.9% ($p < 0.001$) in pain scores before PBMT and 15.2% ($p = 0.040$) immediately after PBMT (Table 3).

In the contralateral medial pterygoid on days 1 ($p = 0.039$) and 4 ($p = 0.038$) immediately after PBMT, there was a reduction in mean pain scores on palpation. In the ipsilateral medial pterygoid, there was a mean daily reduction of 49.7% ($p < 0.001$) in pain scores before PBMT and 39.4% ($p < 0.001$) immediately after PBMT over the 28 days of evaluation. In the contralateral temporal, there was a mean daily reduction of 17.7% ($p = 0.025$) in pain scores before PBMT over the 28-day evaluation (Table 3).

In the TMJ, PBMT reduced pain immediately after application significantly on days 2 ($p = 0.026$) and 3 ($p = 0.011$). In the ipsilateral TMJ, there was a mean daily reduction of 25.0% ($p = 0.007$) in pain scores before PBMT and in the contralateral TMJ of 23.4% ($p = 0.009$), ranging from 1.75 ± 2.30 and 0.81 ± 2.07, respectively, to 1.25 ± 2.50 and 0.00 ± 0.00 (Table 5).

Influence of dosimetry pain in masticatory muscles, TMJ, and during mouth opening

No one dosimetry characteristic showed significant correlation with initial maximum mouth opening, but the minimum dose in ipsilateral masseter muscle ($p = 0.045$) and in ipsilateral TMJ ($p = 0.015$) and the average ($p = 0.028$) and maximum ($p = 0.030$) dose in TMJ were directly correlated with pain during mouth opening (Supplementary material 1).

Table 2 Dosimetric characteristics of patients with head and neck radiotherapy-related trismus treated with PBMT

Patient	Ipsilateral lateral pterygoid			Contralateral lateral pterygoid			Ipsilateral medial pterygoid			Contralateral medial pterygoid			Ipsilateral masseter			Contralateral masseter			Ipsilateral temporal			Contralateral temporal			Ipsilateral TMJ			Contralateral TMJ		
	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max	Min	Mean	Max
1	97	101.5	105	42.6	73.9	98.8	98.5	100.8	103.4	85.1	92.3	103.5	45.4	92.4	107	23.6	55.3	88.9	1.4	44.5	104.9	0	26.1	94.4	83.6	98.7	104.4	33.1	43.5	68.4
2	100.9	101.9	103.5	54.1	79.9	91.5	94.7	101.7	103.4	82.4	87.2	90.1	46.1	63.2	85.9	101.1	102.1	103.3	0.4	13.9	103.2	0.4	8.4	79.1	NA	NA	NA	28.2	47.9	70.8
3	51.8	92.5	102.9	27.1	70.2	87.8	97	102.5	105.5	77.2	88.7	102.6	16.5	60.4	96.9	13.3	49	91.1	1.9	24.9	101.8	2.1	18.7	83.3	19.1	44.9	84.9	15.7	28	60.5
4	3.4	9.7	41.4	4	17.5	77.4	4.2	46.4	99.2	6.3	54.9	100.9	1.8	25.7	79.4	2.2	33.7	70.7	0.3	1.2	14.6	0.3	1.2	13.4	1.8	2.2	2.6	2.6	4.4	8.1
5	30.1	71.8	102.9	26.9	57.2	94.3	94.1	102.6	104.6	69.1	91.3	103.7	22.8	59.8	94.4	17	44.6	74.8	0	15.7	102.5	0	11.6	69.9	28.3	44.7	69.4	19.9	32.4	57.7
6	53.3	95.6	102.4	51.6	88.8	100.3	98.2	100.4	102.3	90.6	99.4	102.2	20.3	60.1	96.2	25.8	56.6	79.1	0.4	20	101.2	0.1	18.1	93.7	39.6	70.3	99.9	40	68.2	89
7	3.6	8.2	69	3.7	6.4	28.5	5.2	67.8	102.5	5.2	61.6	99.1	2.9	48.5	102	2.9	62.7	104.3	0.1	1.5	23.7	0.1	1.3	10.6	2.6	3.3	4.3	2.3	3.1	4.1
8	100.3	101.7	102.8	47.2	80.5	90.7	96.2	101.5	103.9	76.2	86.2	90	38.5	94.6	103.2	22.2	79.3	104.4	0.1	24.9	105.6	0	9.6	84.9	81.1	96.7	102.9	23.5	55.7	97.8
9	96.9	102.4	103.9	23.5	34.8	52.2	95	101.2	104.5	15.1	29.9	63.8	81.9	99	104.2	11.5	18.2	37.6	1.2	54.7	106	0.7	14.8	46.4	71	86.8	100.3	19.6	30.3	35.8
10	38	70.9	102.4	40.3	65.1	84.1	90.6	99.9	103.8	82	88.9	95.9	22.2	75.7	104.8	18.8	45.1	74.4	0.7	5.3	45.4	0.8	6.2	46.7	26.4	40.3	65.7	29.8	45.1	73.5
11	48.1	80.8	102.8	13.7	29.3	39	2.3	45.3	102.6	3.6	26.5	41	NA	NA	NA	2.3	15.3	19.6	0.3	14.1	94.2	0.2	5	22.9	23.8	44.1	52.2	10.4	14.1	16.1
12	21.1	57.6	99.9	23.6	49.2	79.5	75.2	101.8	108.6	58.7	80.6	97.6	19.9	62	101.4	20.7	33.3	67.3	0.4	7.3	76.3	0	5.6	44.7	18.2	24.9	43.2	23.5	34.2	53.8
13	94.4	103.6	106.3	29.5	40.1	68.5	91.9	104.2	107.2	44.5	91	100.3	103	104.6	106.9	25.2	50.9	92.3	2.4	43	106.8	1.7	14.9	64	103.5	105.4	106.4	30.6	36.8	40.2
14	3.1	4.5	7.6	2.7	4.1	7.4	4.6	6	8.2	3.8	5.4	8.1	12.7	85.8	106.1	22.7	61.6	94.3	1.6	2.3	3.3	1.1	1.8	3.1	2.6	3.3	4.1	1.7	2.2	3.1
15	23.1	49.1	98.3	19.3	41.7	84.7	88.4	100.9	106.9	68.7	90.2	101.8	15.2	56.5	95.8	13.7	41	65.6	0.8	4.6	44.7	0.9	3.9	31.1	NA	NA	NA	24.9	34.7	45.5
16	44.9	78.5	104.6	38.2	71.7	102.2	90.1	100.3	104.4	84.5	100.6	104.3	22.1	56.8	93	23.3	46.9	81.7	2.2	9.9	72	1.1	8.3	78.1	45.2	61.1	74.4	27.7	42.4	69.5
Mean	50.6	70.6	91.0	28.0	50.7	74.2	70.4	86.5	98.2	53.3	73.4	87.8	31.4	69.7	98.5	21.6	49.7	78.1	0.9	18.0	75.4	0.6	9.7	54.1	39.1	51.9	65.3	20.8	32.7	49.6
SD	36.7	35.5	28.0	16.7	27.0	28.0	39.9	29.3	24.1	34.3	29.2	27.3	28.2	21.7	8.0	22.7	21.4	23.4	0.8	16.6	36.8	0.6	7.2	31.0	33.2	36.1	38.8	11.6	19.0	29.7

Min, minimum RT dose; *Mean*, mean RT dose; *Max*, maximum RT dose; *SD*, standard deviation; *TMJ*, temporomandibular joint; *NA*, not available

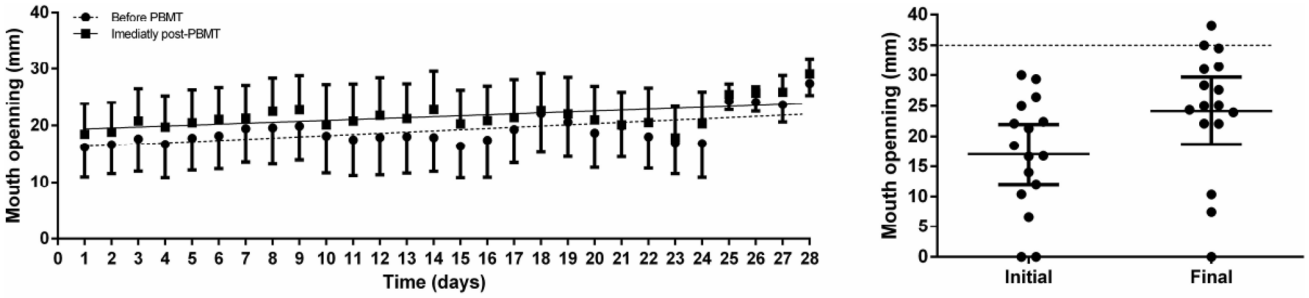

Fig. 3 Daily mouth opening average during PBMT application

The minimum ($p=0.031$) and average ($p=0.014$) radiation doses in ipsilateral pterygoid muscle, the minimum dose in ipsilateral masseter muscle ($p=0.003$), the maximum dose in ipsilateral temporal muscle ($p=0.040$), and the average ($p=0.022$) and maximum ($p=0.025$) radiation doses in contralateral TMJ were directly correlated with the pain in ipsilateral masseter muscle. The pain in contralateral masseter muscle was directly correlated with the maximum radiation dose in ipsilateral temporal muscle ($p=0.045$) and pain in ipsilateral temporal muscle was inversely correlated with average ($p=0.022$) and maximum ($p=0.009$) radiation dose in contralateral masseter muscle (Supplementary material 1).

The gain in mouth opening was inversely correlated with minimum ($p=0.044$), average ($p=0.029$), and maximum ($p=0.024$) radiation doses in ipsilateral medial pterygoid muscle and with the average dose in medial contralateral media pterygoid muscle ($p=0.047$). The minimum radiation dose in ipsilateral masseter muscle ($p=0.022$), the average radiation doses in ipsilateral and contralateral temporal muscles ($p=0.021$, $p=0.035$, respectively), the maximum radiation doses in ipsilateral and contralateral temporal muscles ($p=0.029$, $p=0.039$, respectively), and minimum TMJ dose in ipsilateral TMJ ($p=0.042$) and maximum dose in contralateral TMJ ($p=0.044$) also were inversely correlated with mouth opening gain (Supplementary material 1).

Additionally, maximum mouth opening before the start of PBMT treatment was inversely correlated with pain in the contralateral masseter, ipsilateral and contralateral temporal, contralateral pterygoid, ipsilateral, and contralateral TMJ ($p<0.001$). Pain in all structures was directly correlated with each other ($p<0.001$) (Supplementary material 1).

Discussion

This work is the first clinical trial that evaluated the effectiveness of PBM as a form of treatment for trismus in patients with head and neck cancer during RT. Sixteen patients were included in the study, of which 15 showed significant improvement in mouth opening throughout radiation therapy. There was a reduction of pain on palpation in the masticatory muscles ipsilateral to the entrance of the radiation beam and both TMJ bilaterally.

An extensive literature review has shown that the development of trismus in patients with the head and neck cancer occurs initially after head and neck radiotherapy, lasting for months after the end of treatment [11]. In our study, the patients had their development between the 2nd to 24th radiotherapy session. Although it is a late sequela of head and neck RT, we observed the risk of its development during treatment and that it cannot be neglected.

The mean total radiation dose used was 65 Gy, ranging from 53 to 70 Gy, which is common in the treatment of patients with the head and neck cancer. The dosimetric study showed that the medial pterygoid and ipsilateral masseter muscles were the structures that received the highest doses of radiation and the contralateral temporal muscles received the lowest dose, as well as the contralateral TMJ where it received the lowest maximum dose. All structures contralateral to the entrance of the radiation beam received doses lower than the ipsilateral structures; however, these had maximum doses above 40 Gy, where the risk of developing trismus from this dose is already described in the literature [21–23].

In our study, we could observe that during radiotherapy radiation generates pain in the muscles, mainly in the masseter and medial pterygoid muscles, which are also the muscles that received the most radiation; we suggest that this pain in the muscles reflects in a decompensated mouth opening reflecting in a disorder in the ATM region. Where even receiving low doses of radiation, it was still exposed to doses that provide a risk of reduced mouth opening later. In addition, muscle pain can generate discomfort, consequently contributing to the decrease in maximal mouth opening [23].

Another finding in our study is that the higher the radiation dose to the temporalis and lateral pterygoid muscles, the lower the clinical benefit of the laser, probably because there is a continuous inflammatory stimulus in the structures and the laser, even daily, can only control

Table 3 VAS-scale pain in masticatory muscles in patients with head and neck radiotherapy-related trismus treated with PBMT

	Masseter						Temporal						Medial pterygoid					
	Ipsilateral		*p* value[a]	Contralateral		*p* value[a]	Ipsilateral		*p* value[a]	Contralateral		*p* value[a]	Ipsilateral		*p* value[a]	Contralateral		*p* value[a]
	Pre-PBMT	Post-PBMT		Pre-PBMT	Post-PBMT		Pre-PBMT	Post-PBMT		Pre-PBMT	Post-PBMT		Pre-PBMT	Post-PBMT		Pre-PBMT	Post-PBMT	
D1	2.69 ± 2.72	2.23 ± 2.74	0.109	0.88 ± 1.89	0.75 ± 1.44	0.593	1.60 ± 3.02	1.00 ± 2.65	0.180	0.31 ± 1.25	0.13 ± 0.50	0.317	3.08 ± 3.63	2.92 ± 3.58	0.317	1.50 ± 2.03	1.00 ± 1.63	***0.039***
D2	1.62 ± 2.96	1.54 ± 2.79	0.713	0.88 ± 2.55	0.56 ± 1.36	0.461	1.93 ± 3.20	1.20 ± 2.83	0.066	1.06 ± 2.72	0.50 ± 1.41	0.102	2.83 ± 3.79	2.17 ± 3.27	0.109	1.00 ± 2.50	0.50 ± 1.41	0.216
D3	1.69 ± 2.90	1.38 ± 2.81	0.102	0.50 ± 1.41	0.44 ± 1.31	0.655	1.07 ± 2.40	0.40 ± 1.30	0.102	0.00 ± 0.00	0.00 ± 0.00	1.000	3.00 ± 3.59	1.50 ± 2.15	0.066	0.63 ± 1.54	0.25 ± 1.00	0.180
D4	2.62 ± 3.43	1.69 ± 2.29	0.068	0.31 ± 1.25	0.38 ± 0.89	0.785	1.33 ± 3.06	0.67 ± 1.59	0.273	0.31 ± 1.25	0.56 ± 1.63	0.655	3.25 ± 3.93	2.83 ± 3.83	0.102	0.88 ± 1.71	0.38 ± 1.02	***0.038***
D5	2.23 ± 3.06	1.23 ± 1.83	***0.026***	0.44 ± 1.31	0.38 ± 0.89	0.785	1.27 ± 3.03	1.27 ± 2.37	1.000	0.31 ± 1.25	0.81 ± 2.56	0.655	2.92 ± 3.60	2.17 ± 3.21	0.109	0.50 ± 1.32	0.25 ± 0.77	0.102
D6	1.69 ± 2.50	1.00 ± 1.63	0.102	0.38 ± 1.02	0.50 ± 1.32	0.854	1.93 ± 3.56	0.87 ± 2.13	0.068	0.88 ± 1.89	0.44 ± 1.31	0.581	3.00 ± 3.38	1.75 ± 2.05	0.066	0.50 ± 1.15	0.38 ± 1.26	0.715
D7	1.62 ± 2.14	1.23 ± 1.79	0.059	0.19 ± 0.75	0.31 ± 0.87	0.317	1.67 ± 3.13	0.93 ± 2.15	0.357	0.56 ± 2.25	0.00 ± 0.00	0.317	2.00 ± 2.76	1.67 ± 2.35	0.102	0.50 ± 1.41	0.38 ± 1.26	0.317
D8	1.92 ± 1.88	1.17 ± 1.34	0.131	0.40 ± 1.06	0.40 ± 0.83	1.000	0.93 ± 2.20	0.71 ± 1.98	0.180	0.47 ± 1.25	0.40 ± 1.12	0.317	2.00 ± 2.37	1.58 ± 2.43	0.102	0.67 ± 1.18	0.60 ± 1.12	0.317
D9	2.50 ± 3.29	1.75 ± 2.86	0.066	0.47 ± 1.25	0.47 ± 0.99	1.000	0.71 ± 1.82	0.29 ± 1.07	0.180	0.47 ± 1.25	0.13 ± 0.52	0.180	1.92 ± 2.23	1.42 ± 1.88	0.157	0.60 ± 1.24	0.53 ± 1.13	0.317
D10	1.20 ± 1.75	0.60 ± 1.07	0.083	0.42 ± 1.00	0.42 ± 1.00	1.000	0.27 ± 0.65	0.64 ± 2.11	0.655	0.00 ± 0.00	0.00 ± 0.00	1.000	1.50 ± 2.32	1.10 ± 1.85	0.157	0.25 ± 0.87	0.17 ± 0.58	0.317
D11	1.20 ± 1.87	0.90 ± 1.91	0.257	0.55 ± 1.29	0.91 ± 1.64	0.414	0.70 ± 2.21	0.50 ± 1.58	0.317	0.36 ± 1.21	0.27 ± 0.90	0.317	1.50 ± 1.65	1.10 ± 1.45	0.285	0.82 ± 1.40	0.64 ± 1.43	0.655
D12	0.80 ± 1.48	0.50 ± 1.27	0.180	0.73 ± 1.27	0.64 ± 1.29	0.854	0.60 ± 1.58	0.40 ± 1.26	0.157	0.45 ± 1.51	0.64 ± 1.57	0.317	1.70 ± 2.06	0.60 ± 1.07	0.066	0.73 ± 1.68	0.27 ± 0.90	0.317
D13	1.50 ± 2.07	0.90 ± 1.91	0.180	0.27 ± 0.90	0.55 ± 1.04	0.180	1.00 ± 2.16	0.90 ± 1.91	0.317	0.73 ± 1.62	0.73 ± 1.62	1.000	1.80 ± 2.04	0.80 ± 1.14	0.129	0.73 ± 1.35	0.27 ± 0.65	0.180
D14	0.80 ± 1.48	0.40 ± 1.26	0.180	0.30 ± 0.95	0.50 ± 1.08	0.317	0.50 ± 1.58	0.50 ± 1.58	1.000	0.40 ± 1.26	0.40 ± 1.26	1.000	1.11 ± 1.27	0.78 ± 1.09	0.257	0.67 ± 1.41	0.56 ± 1.13	0.317
D15	0.70 ± 1.34	0.50 ± 1.27	0.157	0.50 ± 1.08	0.50 ± 1.08	1.000	0.70 ± 1.89	0.60 ± 1.58	0.317	0.60 ± 1.58	0.50 ± 1.27	0.317	1.33 ± 1.66	0.78 ± 1.20	0.102	0.78 ± 1.30	0.33 ± 1.00	0.180
D16	1.33 ± 1.73	0.89 ± 1.54	0.102	1.00 ± 1.80	0.56 ± 1.13	0.357	0.67 ± 1.66	0.67 ± 1.66	1.000	0.67 ± 1.66	0.56 ± 1.33	0.317	1.50 ± 2.14	1.50 ± 2.27	1.000	0.88 ± 1.64	0.88 ± 1.64	1.000
D17	1.56 ± 1.74	1.22 ± 1.39	0.180	0.67 ± 1.41	0.78 ± 1.20	0.655	0.67 ± 2.00	0.67 ± 2.00	1.000	0.56 ± 1.67	0.44 ± 1.33	0.317	1.25 ± 1.58	1.13 ± 1.55	0.317	0.88 ± 1.64	0.88 ± 1.64	1.000
D18	1.44 ± 1.59	0.67 ± 1.12	0.102	0.67 ± 1.32	0.67 ± 1.41	1.000	0.89 ± 2.03	0.78 ± 1.72	0.317	0.78 ± 1.72	0.67 ± 1.41	0.317	1.25 ± 1.28	0.88 ± 1.13	0.180	0.88 ± 1.64	0.75 ± 1.39	0.317
D19	1.67 ± 2.12	0.89 ± 1.54	***0.038***	0.44 ± 1.33	0.44 ± 0.88	1.000	0.78 ± 2.33	0.67 ± 2.00	0.317	0.56 ± 1.67	0.56 ± 1.67	1.000	1.50 ± 1.41	1.50 ± 1.41	0.705	0.88 ± 1.36	0.75 ± 1.16	0.317
D20	2.44 ± 2.19	1.33 ± 1.94	***0.041***	0.78 ± 1.72	0.56 ± 1.13	0.564	1.11 ± 2.26	0.89 ± 1.76	0.317	1.00 ± 2.00	0.78 ± 1.56	0.317	1.88 ± 1.89	1.38 ± 1.41	0.655	1.13 ± 1.89	0.75 ± 1.49	0.083
D21	1.67 ± 2.06	0.56 ± 1.33	0.063	1.00 ± 1.58	0.56 ± 1.13	0.357	1.22 ± 2.22	0.89 ± 1.76	0.180	1.00 ± 2.00	0.89 ± 1.76	0.317	1.75 ± 2.31	1.25 ± 1.75	0.102	1.13 ± 1.89	0.75 ± 1.39	0.180
D22	1.43 ± 1.81	0.86 ± 1.46	0.194	0.86 ± 1.86	0.71 ± 1.25	0.785	1.14 ± 2.27	1.00 ± 1.91	0.317	1.14 ± 2.27	1.00 ± 1.91	0.317	1.00 ± 1.26	0.67 ± 1.21	0.157	0.67 ± 1.21	0.50 ± 1.22	0.317
D23	2.14 ± 2.97	2.00 ± 3.21	0.655	0.71 ± 1.89	1.00 ± 1.53	0.414	1.14 ± 2.27	1.14 ± 2.27	1.000	1.00 ± 1.91	0.86 ± 1.57	0.317	1.33 ± 1.21	0.67 ± 1.21	0.102	0.50 ± 1.22	0.60 ± 1.34	1.000
D24	1.83 ± 2.14	1.50 ± 1.97	0.157	0.50 ± 1.22	1.00 ± 1.67	0.180	1.17 ± 2.40	1.17 ± 2.40	1.000	0.83 ± 1.60	0.83 ± 1.60	1.000	2.67 ± 2.80	0.83 ± 1.17	0.109	0.67 ± 1.21	0.67 ± 1.21	1.000
D25	1.00 ± 2.24	1.00 ± 2.24	1.000	0.00 ± 0.00	0.40 ± 0.89	0.317	0.00 ± 0.00	0.00 ± 0.00	1.000	0.00 ± 0.00	0.00 ± 0.00	1.000	1.00 ± 1.00	0.60 ± 0.89	0.157	0.20 ± 0.45	0.00 ± 0.00	0.317
D26	0.00 ± 0.00	0.00 ± 0.00	1.000	0.20 ± 0.45	0.40 ± 0.89	0.655	0.00 ± 0.00	0.00 ± 0.00	1.000	0.00 ± 0.00	0.00 ± 0.00	1.000	0.60 ± 0.89	0.60 ± 0.55	1.000	0.00 ± 0.00	0.20 ± 0.45	0.317
D27	0.00 ± 0.00	0.00 ± 0.00	1.000	0.00 ± 0.00	0.00 ± 0.00	1.000	0.25 ± 0.50	0.00 ± 0.00	0.317	0.00 ± 0.00	0.00 ± 0.00	1.000	2.25 ± 3.86	0.25 ± 0.50	0.317	0.25 ± 0.50	0.00 ± 0.00	0.317
D28	0.00 ± 0.00	0.00 ± 0.00	1.000	0.00 ± 0.00	0.00 ± 0.00	1.000	0.00 ± 0.00	0.00 ± 0.00	1.000	0.00 ± 0.00	0.00 ± 0.00	1.000	0.50 ± 1.00	2.25 ± 3.86	0.655	0.00 ± 0.00	0.00 ± 0.00	1.000
	p = 0.002[b]	***p = 0.003***[b]		$p = 0.264$[b]	$p = 0.766$[b]		***p < 0.001***[b]	***p = 0.040***[b]		$p = 0.987$[b]	$p = 0.609$[b]		***p < 0.001***[b]	***p < 0.001***[b]		***p = 0.025***[b]	$p = 0.481$[b]	
	$r^2 = 0.312$	***$r^2 = 0.285$***		$r^2 = 0.048$	$r^2 = 0.001$		***$r^2 = 0.389$***	***$r^2 = 0.152$***		$r^2 = 0.001$	$r^2 = 0.010$		***$r^2 = 0.497$***	***$r^2 = 0.393$***		***$r^2 = 0.177$***	$r^2 = 0.026$	

Data showed as mean ± SD

[a] $p < 0.05$, Wilcoxon test / Significant Data in Bold

[b] Spearman correlation / Significant Data in Bold

Table 4 Mouth opening and pain during mouth opening in patients with head and neck radiotherapy-related trismus treated with PBMT

	Mouth opening				Pain during mouth opening				Pain vs. mouth opening[c]
	Pre-PBMT	Post-PBMT	*p* value[a]	Δ	Pre-PBMT	Post-PBMT	*p* value[b]	Δ	
D1 ($n=16$)	16.97 ± 9.36	18.48 ± 10.09	***0.015***	1.51 ± 2.19	4.60 ± 3.44	3.53 ± 3.70	***0.002***	−1.07 ± 1.62	$p=0.557$ ($r=-0.165$)
D2 ($n=16$)	17.52 ± 9.01	18.85 ± 9.75	***0.009***	1.33 ± 1.76	3.27 ± 3.61	2.53 ± 3.18	***0.008***	−0.73 ± 1.39	$p=0.815$ ($r=-0.066$)
D3 ($n=16$)	18.74 ± 9.83	20.77 ± 10.81	***0.007***	2.03 ± 2.62	3.40 ± 3.36	3.00 ± 3.44	***0.005***	−0.40 ± 0.63	$p=0.719$ ($r=-0.101$)
D4 ($n=16$)	17.72 ± 10.33	19.71 ± 10.37	***0.001***	2.00 ± 1.82	3.40 ± 3.48	3.13 ± 3.18	***0.003***	−0.27 ± 0.59	$p=0.107$ ($r=-0.433$)
D5 ($n=16$)	18.92 ± 9.70	20.47 ± 10.95	0.065	1.56 ± 3.13	2.87 ± 3.42	2.27 ± 2.60	***0.007***	−0.60 ± 1.40	$p=0.618$ ($r=-0.140$)
D6 ($n=16$)	19.16 ± 10.32	21.07 ± 10.60	***0.003***	1.91 ± 2.13	2.47 ± 2.26	2.00 ± 2.30	***0.005***	−0.47 ± 0.92	$p=0.909$ ($r=0.032$)
D7 ($n=16$)	20.67 ± 10.21	21.29 ± 10.85	0.057	0.61 ± 1.19	2.13 ± 2.50	1.38 ± 2.16	***0.011***	−0.75 ± 1.48	$p=0.694$ ($r=-0.107$)
D8 ($n=14$)	20.84 ± 11.07	22.49 ± 11.02	***< 0.001***	1.67 ± 1.32	2.14 ± 2.35	1.27 ± 2.12	***0.011***	−0.79 ± 1.19	$p=0.580$ ($r=-0.162$)
D9 ($n=14$)	21.10 ± 10.44	22.76 ± 11.29	***< 0.001***	1.80 ± 1.36	2.64 ± 3.48	2.00 ± 3.40	***0.018***	−0.50 ± 1.34	$p=0.153$ ($r=-0.420$)
D10 ($n=12$)	19.38 ± 11.71	20.12 ± 13.35	0.493	0.74 ± 3.59	2.08 ± 2.61	1.42 ± 2.23	***0.027***	−0.67 ± 1.87	***$p=0.032$ ($r=-0.619$)***
D11 ($n=11$)	18.79 ± 11.35	20.79 ± 12.24	***0.001***	1.99 ± 1.36	2.27 ± 2.53	1.45 ± 2.46	***0.027***	−0.82 ± 1.66	$p=0.330$ ($r=-0.324$)
D12 ($n=11$)	19.53 ± 11.51	21.79 ± 12.41	***0.005***	2.26 ± 2.10	1.36 ± 2.25	1.00 ± 2.10	0.066	−0.36 ± 0.67	***$p=0.015$ ($r=-0.708$)***
D13 ($n=11$)	19.82 ± 11.22	21.20 ± 11.52	***0.009***	1.50 ± 1.31	1.73 ± 2.24	0.73 ± 2.10	***0.027***	−1.00 ± 1.41	$p=0.743$ ($r=0.128$)
D14 ($n=9$)	19.28 ± 10.75	22.78 ± 12.72	***0.018***	3.49 ± 3.53	2.00 ± 2.29	1.75 ± 2.38	***0.026***	−0.50 ± 1.07	$p=0.039$ ($r=-0.733$)
D15 ($n=9$)	17.54 ± 10.14	20.27 ± 11.21	***0.009***	2.72 ± 2.37	1.78 ± 2.39	1.38 ± 2.39	***0.042***	−0.63 ± 0.92	$p=0.171$ ($r=0.536$)
D16 ($n=8$)	19.36 ± 11.15	20.85 ± 11.47	0.137	1.50 ± 2.72	2.38 ± 2.83	1.63 ± 2.77	***0.041***	−0.75 ± 1.75	$p=0.280$ ($r=0.436$)
D17 ($n=8$)	19.29 ± 10.90	21.40 ± 12.54	***0.017***	2.11 ± 2.11	1.75 ± 2.31	1.75 ± 2.38	***0.039***	0.00 ± 0.93	$p=0.622$ ($r=-0.207$)
D18 ($n=8$)	22.09 ± 12.77	22.58 ± 12.39	0.455	0.50 ± 1.91	2.38 ± 2.67	2.13 ± 2.30	***0.043***	−0.25 ± 1.16	$p=0.159$ ($r=-0.549$)
D19 ($n=8$)	20.58 ± 11.37	22.01 ± 12.18	***0.020***	1.43 ± 1.48	2.38 ± 2.33	2.13 ± 2.30	***0.027***	−0.25 ± 0.89	$p=0.280$ ($r=0.436$)
D20 ($n=8$)	18.69 ± 11.26	20.99 ± 11.15	***0.023***	2.30 ± 2.24	1.75 ± 2.71	1.38 ± 2.13	0.066	−0.38 ± 0.74	$p=0.924$ ($r=0.045$)
D21 ($n=8$)	19.92 ± 10.18	20.13 ± 10.82	0.169	1.40 ± 2.36	2.13 ± 2.47	1.88 ± 2.10	***0.043***	−0.25 ± 0.89	$p=0.364$ ($r=0.455$)
D22 ($n=6$)	18.00 ± 10.22	20.50 ± 11.50	***0.008***	2.50 ± 1.68	2.17 ± 2.64	2.00 ± 2.61	0.068	−0.17 ± 0.41	$p=0.805$ ($r=0.131$)
D23 ($n=6$)	16.81 ± 9.82	17.86 ± 10.29	0.217	1.04 ± 2.00	2.17 ± 2.32	1.67 ± 2.25	0.066	−0.50 ± 0.84	$p=0.305$ ($r=0.507$)
D24 ($n=6$)	16.81 ± 11.01	20.31 ± 10.50	***0.035***	1.32 ± 0.95	2.17 ± 2.40	2.33 ± 2.25	0.068	0.17 ± 0.98	$p=0.182$ ($r=0.707$)
D25 ($n=5$)	24.31 ± 2.88	25.50 ± 3.42	0.169	1.81 ± 2.01	1.20 ± 1.30	0.60 ± 0.89	0.109	−0.60 ± 0.89	$p=0.225$ ($r=-0.775$)
D26 ($n=5$)	24.10 ± 2.97	25.74 ± 2.11	0.206	1.83 ± 2.28	1.40 ± 1.67	0.80 ± 1.30	0.109	−0.60 ± 0.55	$p=0.553$ ($r=-0.447$)
D27 ($n=4$)	23.69 ± 5.78	25.91 ± 5.46	***0.049***	2.22 ± 0.88	1.50 ± 1.29	1.00 ± 1.15	0.109	−0.50 ± 0.58	$p=0.333$ ($r=-0.866$)
D28 ($n=4$)	27.43 ± 3.94	29.08 ± 5.09	0.168	1.65 ± 1.35	1.50 ± 1.91	0.25 ± 0.50	0.180	−1.25 ± 1.89	$p=0.667$ ($r=0.500$)
	$p<0.001$[d] ***$r^2=0.390$***	***$p=0.002$[d]*** ***$r^2=0.312$***			***$p<0.001$[c]*** ***$r^2=0.538$***	***$p=0.001$[c]*** ***$r^2=0.372$***			

D, day

Data showed as mean ± SD

[a] $p<0.05$, paired *t*-test/ Significant Data in Bold

[b] $p<0.05$, Wilcoxon test/ Significant Data in Bold

[c] $p<0.05$, Spearman correlation/ Significant Data in Bold

[d] Pearson correlation

it to a certain extent. Thus, future studies are necessary to verify the cut-off point where the laser does not bring clinical benefit. In addition, the application of the laser to the muscles requires an adaptation of the distribution of points, since in our study the laser was not applied directly to the lateral pterygoid due to the difficulty of accessing this structure due to the limitation of mouth opening in the patients and in the muscle temporalis, only one stitch was performed in the anterior region due to the difficulty of application in fibers installed in the scalp region, where absorption is difficult [24]. However, future studies are needed to verify the cut-off point where the laser does not bring clinical benefit.

From this point of view, we realized that radiotherapy actually interferes with oral functionality, although many studies report trismus as a late adverse effect due to fibrosis, in our study we could see that during treatment, inflammatory stimuli daily accumulate in the muscles and the neural level, causing discomfort during radiotherapy, favoring the reduction of mouth opening during treatment, which may also contribute to a future picture of progressive fibrosis [23].

Table 5 VAS-scale pain in temporomandibular joint in patients with head and neck radiotherapy-related trismus treated with PBMT

	Ipsilateral TMJ			Contralateral TMJ		
	Pre-PBMT	Post-PBMT	*p* value	Pre-PBMT	Post-PBMT	*p* value
D1	1.75 ± 2.30	1.17 ± 1.99	0.141	0.81 ± 2.07	0.13 ± 0.50	0.109
D2	3.00 ± 3.38	1.83 ± 3.33	***0.026****	1.06 ± 2.57	0.69 ± 1.70	0.357
D3	3.25 ± 2.99	1.33 ± 1.87	***0.011****	0.56 ± 1.36	0.50 ± 1.75	0.785
D4	3.67 ± 4.19	2.58 ± 2.81	0.066	0.81 ± 1.60	0.38 ± 0.89	0.102
D5	2.75 ± 3.25	1.83 ± 3.04	0.066	0.69 ± 1.58	0.25 ± 0.77	0.109
D6	1.77 ± 2.35	1.46 ± 2.37	0.414	0.25 ± 1.00	0.44 ± 1.31	0.655
D7	1.85 ± 2.23	1.46 ± 1.90	0.102	0.63 ± 1.54	0.44 ± 1.26	0.317
D8	1.83 ± 3.04	1.00 ± 1.60	0.059	0.80 ± 1.78	0.40 ± 0.91	0.109
D9	2.00 ± 2.86	1.33 ± 2.15	0.071	1.13 ± 2.47	0.33 ± 0.90	0.109
D10	1.80 ± 2.15	1.20 ± 1.75	0.063	0.33 ± 1.15	0.42 ± 1.44	0.317
D11	0.90 ± 1.73	1.10 ± 1.85	1.000	0.91 ± 3.02	0.73 ± 1.62	0.655
D12	0.90 ± 1.73	0.60 ± 1.58	0.180	0.27 ± 0.90	0.36 ± 1.21	0.317
D13	0.90 ± 1.73	0.00 ± 0.00	0.109	0.36 ± 1.21	0.91 ± 3.02	0.317
D14	0.56 ± 1.67	0.56 ± 1.67	1.000	0.44 ± 1.33	0.56 ± 1.67	0.317
D15	0.78 ± 1.72	0.78 ± 1.72	1.000	0.56 ± 1.67	0.44 ± 1.33	0.317
D16	1.00 ± 1.77	0.75 ± 1.39	0.157	0.63 ± 1.77	0.50 ± 1.41	0.317
D17	1.13 ± 2.10	0.75 ± 1.49	0.180	0.38 ± 1.06	0.50 ± 1.41	0.317
D18	2.13 ± 3.27	1.63 ± 2.77	0.102	0.63 ± 1.77	0.50 ± 1.41	0.317
D19	0.75 ± 1.75	0.75 ± 2.12	1.000	0.63 ± 1.77	0.63 ± 1.77	1.000
D20	1.75 ± 2.25	1.50 ± 2.20	0.317	0.63 ± 1.77	0.50 ± 1.41	0.317
D21	1.00 ± 1.93	0.88 ± 1.81	0.317	0.63 ± 1.77	0.63 ± 1.77	1.000
D22	2.50 ± 3.33	2.33 ± 3.39	0.317	0.83 ± 2.04	0.67 ± 1.63	0.317
D23	2.17 ± 2.48	1.83 ± 2.23	0.157	0.83 ± 2.04	0.83 ± 2.04	1.000
D24	1.83 ± 2.23	1.50 ± 2.35	0.317	0.83 ± 2.04	0.83 ± 2.04	1.000
D25	2.00 ± 4.47	2.00 ± 4.47	1.000	0.00 ± 0.00	0.00 ± 0.00	1.000
D26	0.80 ± 1.79	0.80 ± 1.79	1.000	0.00 ± 0.00	0.00 ± 0.00	1.000
D27	0.00 ± 0.00	0.00 ± 0.00	1.000	0.00 ± 0.00	0.00 ± 0.00	1.000
D28	1.25 ± 2.50	1.25 ± 2.50	1.000	0.00 ± 0.00	0.00 ± 0.00	1.000
	p = 0.007*	$p = 0.336$		***p = 0.009****	$p = 0.512$	
	r^2 ***= 0.250***	$r^2 = 0.036$		r^2 ***= 0.234***	$r^2 = 0.016$	

*$p < 0.05$, Wilcoxon test (mean ± SD) /Significant Data in Bold and with *

The site of primary tumor involvement, tumor staging, previous surgery or chemotherapy associated with RT treatment, and the presence of the residual disease did not significantly influence the gain of mouth opening. However, most patients had some tumor involvement in the masticatory muscles. These had a lower mean increase of mouth opening than patients with no tumor involvement since PBMT was not applied in these regions of tumor involvement.

The involvement of masticatory muscles is a decisive risk factor for the development of trismus since this can induce muscle compression, invasion, and malfunction and, consequently, reduced jaw movements, leading to pain and making contralateral movement impossible. Moreover, the maximum dose of radiation that surrounds the tumor directly reaches the muscle tissue. Even the use of therapeutic modalities that are highly sparing of healthy tissue, such as IMRT, end up not being able to preserve these structures efficiently [20, 24].

Our study showed that the use of PBM for the treatment of trismus was considerably effective. Although only three patients were able to get out of a mouth opening condition < 35 mm, the average initial mouth opening of the patients increased by more than 7 mm throughout treatment. Of the 16 patients included, only one patient showed no improvement in mouth opening. The average of 45 mm of mouth opening is considered a norm for the population; having a mouth opening of 35 mm is a minimum average for well-being and quality of life [8].

In this study, we highlight the importance of introducing treatment methods in which, although only three patients reach a minimum average mouth opening, providing a 7-mm increase over the course of treatment is significant for an improvement in the quality of life of this population.

Pain in patients with HNC is expected before, during, and after oncologic treatment and is strongly associated with the presence of the tumor and surgical and radiotherapeutic treatment. Usually, the pain is acute during treatment and extends up to 3 months after its termination but may make it impossible to continue therapy, especially radiotherapy [25, 26].

According to the VAS scale, the patients presented pain scores in the masticatory muscles with an average (mild) 1–3. Interestingly, we observed their immediate significant reduction after some PBM sessions on the ipsilateral side, suggesting that it has an analgesic role initially. However, what draws more attention is that all the muscles, except for the medial pterygoid muscle, had their pain scores at 0 on the last day, both before and after PBM, suggesting that PBM has an anti-inflammatory action throughout the applications and, as a consequence, acts by reducing the pain in these patients. Finally, it is worth mentioning that no patient had their radiotherapy treatment interrupted during PBM application.

The damage to muscle tissue generates a loss of myocyte conformity that is highly sensitive to morphological changes, leading to severe impairment in muscle function. These alterations in the cell structure are due to a process of muscle inflammation, producing cytokines and reactive oxygen species. Due to the daily irradiation of the muscles, this process is persistent throughout the radiotherapy treatment, intensifying with each radiotherapy session and lasting for extended periods [23]. Thus, PBM significantly reduced the muscle inflammatory process and provided some repair of the tissue injured daily by RT [27, 28].

Pain in the TMJ region, in turn, showed a reduction not only on the ipsilateral side at the entrance of the radiation beam but also on the contralateral side throughout the PBM protocol. In the TMJ, both sides act simultaneously to perform the rotation and translation movements of the mandible, and its dysfunction on one side generates compensatory disorder in the entire mandibular structure [26, 29–32].

The major limitation of this study is the absence of a placebo-controlled control group. However, due to the continuous worsening of RT-induced trismus and the possibility of having to suspend RT and probe patients because of limited mouth opening, we ethically chose not to conduct a placebo control group. Another limitation is the impossibility of applying PBM to muscles with tumor involvement, which reduces the clinical benefit of PBM in the treatment of RT-related trismus.

However, even with a small sample, we can describe a significant clinical benefit in the treatment of RT-related trismus. Some previous studies conducted for the treatment of side effects in patients with head and neck cancer showed the great effectiveness of PBMT such TMJ pain, trismus, oral mucositis, radiation dermatitis, dysphagia, xerostomia, dysgeusia, osteonecrosis, head and neck lymphedema, and voice/speech alterations due to local inflammation [33, 34]. A study with a sample of 70 patients where the authors compared therapies previously considered gold standard for the treatment of trismus in patients with head and neck cancer with the adjunct of PBMT noting that the group receiving the PBM treatment showed a significant improvement with the gain in mouth opening and reduction in pain scores in the TMJ region [35].

In our work, we were able to show that the analgesic action on the muscles brings some immediate benefits after PBM. Even so, the long-term effect suggests that the control of the muscular anti-inflammatory process resulting from the PBM in the irradiated muscles is the main responsible for improving the mouth opening limitation and the pain during mouth opening. New clinical trials including additional wavelengths, randomized, and preferably placebo-controlled are needed to evaluate the preventive capacity of this or other PBM protocols in RT-related trismus in HNC.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10103-023-03920-0.

Author contribution MMFB: performed inclusion of patients and application of the PBMT protocol; CENM: actively participated in the clinical evaluation of patients regarding pain scores and assessment of the degree of severity of trismus; ACAMC: collected clinical, pathological, and sociodemographic data; AAC: actively participated in writing the article; JFBdM and LMR: reviewed the writing and contributed to the dosimetry analysis; BCC: performed the dosimetry analysis; CGPdA: conducted the final revision of the article; PGdBS: performed the statistical analysis and final review of the study.

Declarations

Ethical approval This study was approved by the ethics committee at the Instituto do Câncer do Ceará protocolaco with 5,182,796.

Informed consent Data collected after participants signed the informed consent form and agreed to participate in the study.

Conflict of interest The authors declare no competing interests.

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