Supportive Care in Cancer
https://doi.org/10.1007/s00520-020-05607-6

ORIGINAL ARTICLE

Cost-effectiveness randomized clinical trial on the effect of photobiomodulation therapy for prevention of radiotherapy-induced severe oral mucositis in a Brazilian cancer hospital setting

Allisson Filipe Lopes Martins[1] · Túlio Eduardo Nogueira[2] · Marília Oliveira Morais[3] · Sebastião Silvério de Sousa-Neto[1] · Angélica Ferreira Oton-Leite[3] · Marize Campos Valadares[4] · Nilceana Maya Aires Freitas[5] · Cláudio Rodrigues Leles[2] · Elismauro Francisco Mendonça[2]

Received: 15 April 2020 / Accepted: 26 June 2020

Abstract

Objectives This study aimed to assess the cost-effectiveness of photobiomodulation therapy (PBMT) in association with a Preventive Oral Care Program (POCP) compared with POCP alone in the treatment of radiotherapy (RT)-induced oral mucositis (OM).

Methods The cost-effectiveness was evaluated from the health provider perspective and conducted alongside a randomized, double-blind clinical trial. Participants were randomly assigned to either PBMT ($n = 25$) or control ($n = 23$) group. The PBMT group participants received PBMT associated with POCP. In the control group, patients were submitted to POCP alone. Costs were identified, quantified, and valued through observation and consultation of the hospital's financial sector database and estimated in Brazilian real and converted to international dollars using the purchasing power parity exchange rate. The incremental cost-effectiveness ratio (ICER) was estimated by considering the prevention of severe OM, interruption of RT, and oral health-related quality of life (OHRQoL) scores, measured by the OHIP-14 and patient-reported OM symptoms scale (PROMS).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00520-020-05607-6) contains supplementary material, which is available to authorized users.

✉ Elismauro Francisco Mendonça
elismaur@ufg.br

Allisson Filipe Lopes Martins
allissonfilipe@hotmail.com

Túlio Eduardo Nogueira
tulioenogueira@gmail.com

Marília Oliveira Morais
moraismarilia010@gmail.com

Sebastião Silvério de Sousa-Neto
sebastiaoneto136@gmail.com

Angélica Ferreira Oton-Leite
angelicaothon@hotmail.com

Marize Campos Valadares
marizecv@ufg.br

Nilceana Maya Aires Freitas
nilceanamaya@gmail.com

Cláudio Rodrigues Leles
leles.cr@gmail.com

[1] Laboratory of Oral Pathology, School of Dentistry, Federal University of Goiás, Avenida Universitária Esquina com 1ª Avenida, s/n. Setor Universitário, Goiânia, Goiás CEP 74605-220, Brazil

[2] Department of Prevention and Oral Rehabilitation, School of Dentistry, Federal University of Goiás, Avenida Universitária Esquina com 1ª Avenida, s/n. Setor Universitário, Goiânia, Goiás CEP 74605-220, Brazil

[3] Araujo Jorge Cancer Hospital, R. 239, 206 - Setor Universitário, Goiânia, Goiás CEP 74175-120, Brazil

[4] Laboratory of Pharmacology and Cellular Toxicology, Pharmacy Faculty, Federal University of Goias, 5ª Avenida Esquina com Rua 240, s/n. Setor Universitário, Goiânia, Goiás CEP 74605-170, Brazil

[5] Department of Radiotherapy, Araujo Jorge Cancer Hospital, R. 239, 206–Setor Universitário, Goiânia, Goiás CEP 74175-120, Brazil

Published online: 03 July 2020

Results The incremental cost of PBMT was $857.35, and the cost per session was $25.69. The ICER was $ 2867.39 to avoid one case of severe OM and $ 2756.75 to prevent one interruption in RT due to OM. ICER to reduce 1 point in OHIP-14 and PROMS scores were $170.79 and $31.75, respectively.
Conclusion PBMT is more cost-effective than POCP alone in preventing severe OM, worsening of the OHRQoL, and RT interruptions. PBMT is a promising therapy, especially to avoid interruptions in oncological treatment.
Trial registration ReBEC-RBR-5h4y4n

Keywords Oral mucositis · Photobiomodulation therapy · Low-level laser · Cost-effectiveness · Quality of life

Introduction

Oral mucositis (OM) is one of the main adverse effects of radiotherapy (RT), whether or not associated with chemotherapy (CT), in the treatment of head and neck cancer (HNC). OM is an inflammatory reaction that can affect the entire oral cavity and the gastrointestinal tract [1, 2], and its severity depends on the dose and number of RT sessions [3–5]. Severe OM is often associated with severe pain, increased number of consultations, hospitalizations, treatment interruption, and need for supplemental nutrition. These events could influence patient survival, reduce the patient's quality of life, and increase HNC treatment cost [6–12].

Along with the impacts on the patient's clinical condition and treatment regimen, OM has also meaningful economic implications for the healthcare system. For instance, at a cumulative RT dose of 10 Gy, patients may need topical palliative agents or nonsteroidal anti-inflammatory drugs (NSAIDs) to relieve OM symptoms [5]. It is estimated that OM also leads to a significant increase in the HNC treatment cost, ranging from US$1700 to more than US$40,000, depending on the severity and treatment approach [6, 9, 13]. Increased costs are attributed to increased use of hospital resources, days of hospitalization, and opioid use [14].

Nevertheless, the use of photobiomodulation therapy (PBMT) is reported to reduce incremental costs due to the incidence of severe OM. Bezinelli et al. [10] reported a reduction of up to 30% in overall costs of hematopoietic stem cell transplantation for patients who received PBMT used to prevent and minimize the risk of severe OM. This therapy is recognized as being patient-friendly and well-tolerated, especially to patients who are unable to be submitted to other modalities, such as mouthwashes [15]. In addition, no side effects associated with PBMT are described, except for situations of nonpainful burning sensation. Despite its safety and efficacy, the decision-making of choosing PBMT in OM treatment should consider other issues, such as the cost of the laser device, the need for a license to perform PBMT, dental staff working time, a specific setting for the therapy, and local regulations [15].

However, few studies assessed the economic aspects of the use of PBMT as an adjuvant intervention for the management of OM in HNC treatment. Antunes et al. [14] evaluated the cost-effectiveness of using PBMT for the prevention of severe OM in HNC patients receiving RT concurrent with CT, from the perspective of the Brazilian public health system. Results showed that PBMT had an incremental cost of US$1689 compared with a control group (sham laser beam), and an incremental cost-effectiveness ratio (ICER) of US$4961.37 per additional grade 3–4 OM (severe OM) event prevented. They also recommended further studies to assess the economic impacts of PBMT on patient quality of life outcomes, as a result of the management of OM [14].

There is a need for studies assessing whether it is worth including PBMT as an adjuvant treatment for prevention and control of OM, as well as its impacts on patient-centered outcomes and clinical symptoms. Therefore, this randomized clinical trial aimed to assess the effects of the PBMT associated with standard preventive oral care compared with a preventive oral care program alone in preventing severe OM in patients with HNC receiving RT or combined chemoradiotherapy. Additionally, we assessed the impacts of PBMT on changes in patient's oral health-related quality of life and severity of oral symptoms related to OM during the RT regimen. Finally, a trial-based cost-effectiveness analysis was performed to assess the economic impacts of introducing the PBMT in private healthcare settings as a complementary treatment for the prevention and control of OM.

Materials and methods

This is a randomized, double-blind, placebo-controlled clinical trial that included a cost-effectiveness analysis. A detailed description of the study protocol is published elsewhere [16]. The study protocol was approved by the Ethics Research Committees of the Federal University of Goias, Brazil (Protocol 2.053.687/2017) and the Araujo Jorge Cancer Hospital (Protocol 2.131.323/2017). All participants provided signed, informed consent to participate in the study. The study was also previously registered at the Brazilian Clinical Trials Registry (REBEC; RBR-5h4y4n).

The study setting was the dental care service of a cancer hospital, which includes a dental office and a waiting room, and a dental staff comprising a trained dentist in PBMT and a dental assistant.

Participants

Participants of this study were regular patients of the HNC service of the Araujo Jorge Cancer Hospital in Goiania, Brazil, who were recruited between July 2017 and June 2019. The study interventions and data collection were finished in October 2019.

The prescribed HNC treatment for all participants included conventional RT, 2 Gy/day, five times a week, associated or not with CT. HNC patients with tumors located in the oral cavity, oropharynx, nasopharynx, and with advanced stages of laryngeal tumors were included. All included participants were aged ≥ 18 years, of both genders, and received a minimal overall RT dose of 50 Gy. The exclusion criteria comprise potential confounding conditions that could potentially affect the study results. These criteria are applied in case of potential study participants who meet the inclusion criteria but present additional characteristics not related to the study that could interfere with the success of the interventions or increase their risk of an unfavorable outcome.

Thus, the exclusion criteria comprised the presence of salivary gland disorders (Sjögren syndrome or salivary gland tumors), presence of infectious diseases, or previous treatment with CT or RT in the head and neck area. Additionally, patients under palliative care or those diagnosed as having lymphoma or melanoma, skin cancer, were also excluded. Additionally, patients under palliative care or those diagnosed as having lymphoma or melanoma, skin cancer, were excluded.

Clinical, demographic, and pathological data were retrieved from the patient's medical records.

Sample size estimation was performed considering the incidence of severe OM in patients that were submitted to PBMT and control groups, according to data retrieved from a systematic review [17]. The following parameters were used for sample size calculation: 5% significance level, a study power of 80%, and a 1.0 ratio of unexposed/exposed. An incidence of severe OM of 60% for the control group and 20% for the PBMT group was considered the between-group difference for sample size estimation.

Study groups

The participants were randomly assigned to one of the two study groups: (I) control group—Preventive Oral Care Protocol (POCP) and (II) experimental group—PBMT combined with POCP.

I. Control group (POCP)

The participants of this group received standard preventive oral care (POCP) [18] that comprised elimination of infection focuses, prescription of fluoride rinse 0.05% three times a day, chlorhexidine 0.12% rinse (diluted in water in a 1:1 proportion) three times a day, the recommendation to drink at least 1.5 L of water, and maintenance of good oral hygiene. The use of oral ointment containing a corticoid (topical triamcinolone acetonide, 3 times/day) was prescribed in case of the occurrence of OM.

The patients also received a sham laser procedure, 5 times a week. The laser equipment was turned on, and the characteristic sound of the laser device was emitted, but the laser was not irradiated. At the end of RT or when RT was suspended because of severe OM, the patients in this group received PBMT as an adjuvant treatment.

II. Experimental group (PBMT)

Participants assigned to this group received the standard POCP similarly to the control group, associated with the PBMT protocol, which was delivered 5 times a week between the RT sessions, using an InGaAlP diode laser (Twin Flex Evolution Laser, MMOptics, São Paulo, Brazil).

PBMT parameters were as follows: use of a red laser (660 nm), with a power of 25 mW and deposited energy of 0.25 J per point, or 6.2 J/cm^2, for 10 s; the daily energy applied was 15.25 J. The laser was applied in a continuous mode and punctual and perpendicular in contact with the mucosa; however, the laser was not irradiated in the surgical bed of tumoral resection or near a malignant lesion, if observed. The anatomical points considered for PBMT were according to the study by Oton-Leite et al. [12].

Randomization and blinding/masking

A simple randomization scheme, considering a 1:1 allocation ratio, was produced using a computer-based random number generator (www.randomizer.org). The randomization sequence was generated by an independent collaborator who was blinded to the study groups. The use of letters A and B determined the group (A = PBMT; B = control). Subsequently, the sequence of the assigned groups was concealed in consecutively numbered envelopes. In the first PBMT appointment, immediately before the first RT session, the respective research assistant opened the envelope and allocated the patient to the assigned group. All participants were blinded to their assigned group since all the procedures were similar in both groups, except for the use of real or sham laser beam when using the PBMT equipment. Additionally, OM assessment was performed by one researcher on the basis of photographs of the patients to assure blinding in OM assessment.

Outcomes

Oral mucositis

OM was classified according to the World Health Organization (WHO) [19] and the National Cancer Institute (NCI) scales [20]. The WHO classification scale rates OM on a 5-point ordinal scale ranging from 0 to 4, as follows: "0"—no signs or symptoms; "1"—oral soreness and erythema; "2"—erythema, ulcer, both solid, and liquid diets tolerated; "3"—ulcers and liquid diet only; and "4"—oral feeding is impossible. The NCI scale rates OM on a 6-point ordinal scale ranging from 0 to 5, where "0"—no visible alterations; "1"—asymptomatic or mild symptoms (intervention not indicated); "2"—moderate pain or ulcer that does not interfere with the oral intake (modified diet indicated); "3"—severe pain (interfering with oral intake); "4"—life-threatening consequences (urgent intervention indicated); and "5"—death.

Patients with grades 3 or 4 OM according to the WHO scale and grades 3, 4, or 5 OM according to the NCI scale were considered having severe OM. The number needed to treat (NNT) was calculated considering the two scales (WHO and NCI). For the rating of OM scores, one member of the research team was previously trained and calibrated using clinical photographs of ten patients with OM who were not included in the study. Two repeated assessments were carried out separated by a 90-day time interval. The overall agreement (weighted kappa statistics) for the two scales was 87.5%.

The diagnosis of OM severity was based on the assessment of intraoral pictures of the patients (labial and buccal mucosa, hard and soft palate, lateral surface of the tongue, and floor of mouth) at the first appointment and at the 7th, 14th, 21st, and 30th RT sessions. Dietary information registered in non-identified clinical records was provided to the evaluator.

Oral health-related quality of life

Oral health-related quality of life (OHRQoL) was assessed using the shortened version of the Oral Health Impact Profile (OHIP-14) previously translated, adapted, and validated for Brazilian Portuguese [21, 22]. Additionally, patient-reported symptoms related to OM were assessed using the Brazilian version of the Patient-Reported Oral Mucositis Symptoms (PROMS) scale [18, 23]. The summative score of the scale items was considered the PROMS score. Both questionnaires (OHIP-14 and PROMS) were administered at baseline (before the first appointment) and at the 30th RT session. The difference between the scores of the first and the last evaluations was considered the measure of effectiveness for the OHRQoL and PROMS scales.

Economic analysis

For this study, the economic analysis was performed from the perspective of the health provider. We considered the costs associated with the PBMT protocol and the costs associated with the incidence of severe OM. Personnel costs were limited to the dentist, as hired only for performing the PBMT. The time frame considered for economic evaluation was the RT period. The CHEERS (Consolidated Health Economic Evaluation Reporting Standards) checklist was used for the planning and reporting of the economic analysis of this study. This study was based on a previous cost-effectiveness analysis [14].

Cost estimation

PBMT costs included the direct costs of resources associated with the use of PBMT to prevent/treat OM during the RT regimen. Variable cost items included consumables (70% ethanol, gauze, procedure glove, etc.), and fixed costs included the income of the dental staff and equivalent annual cost (EAC) of the laser equipment. EAC of the laser equipment was calculated by considering a 5% discount rate and a 5-year use.

The clinical time for each PBMT session was registered, and the number of daily appointments was retrieved from the patient's records. The average cost per PBMT session was calculated as the sum of the variable and fixed annual costs divided by the total number of PBMT sessions provided in a 1-year period. For this calculation, we estimated a total of 251 working days a year and an average number of 10 patients receiving PBMT per day. The personnel cost was based on the salary of the members of the staff, informed by the administration of the hospital.

Data on consumable costs were retrieved from the purchasing department of the hospital, whereas data on the cost of the laser equipment was calculated based on the mean market price.

We assumed that the costs of RT, CT, and POCP-related procedures were similar in both groups and were not considered for analysis. Indirect costs related to wider societal costs (e.g., loss of productivity resulting from treatment and family costs) and other capital costs or those associated with the implementation of the dental care service were also not considered.

The additional costs related to the occurrence of severe OM were also calculated. It included visits to the emergency service and hospitalizations, consumable items, medication (nonsteroidal analgesics, corticoids, opioid analgesics), and advanced additional procedures such as nasoenteral intubation, electrolyte replacement, and parenteral nutrition. These data were retrieved from the patient's medical records.

The detailed description of cost items and methods used for quantification, cost estimation, and source of valuing the PBMT and OM-related costs are described in the Supplementary Material. All costs were estimated in Brazilian currency (Brazilian real, BRL) and later converted to international dollars. The international dollar is a hypothetical currency that allows comparisons of costs from one country to the other, using the US dollar as reference [24]. Monetary values in Brazilian currency were converted into international dollars using the Purchasing Power Parity (PPP) exchange rate for the year 2018, which was 2.03 ($ 1 PPP = $ 2.03 BRL) [25].

Cost-effectiveness analysis

The percent of severe degrees of OM that was avoided, in both groups, was considered the measure of effectiveness for the calculation of the ICER. ICER was calculated by dividing the difference in costs (cost2 − cost1) by the difference in the incidence of non-severe OM between the two groups (effectiveness2 − effectiveness1), where "1" is the standard intervention (control) and "2" is the experimental intervention (PBMT group). Thus, ICER value represents the incremental cost to avoid the occurrence of one case of severe OM using PBMT; this calculation was based on previous study [14].

Additionally, ICER was also calculated considering the patient-reported outcomes as the measure of effectiveness, representing the incremental cost to avoid a 1-point reduction in the OHRQoL measure. Two different ICERs were calculated considering the scores of each instrument (OHIP-14 and PROMS). Finally, an ICER was calculated considering the prevention of RT interruption due to OM-related symptoms. This information was retrieved from patients' forms.

A tree-type decision diagram was constructed to represent all clinically relevant events, assuming that OM is an acute, short-term condition that does not recur over time, due to these characteristics [5]. The graphical model of the decision tree described the decisions and their possible outcomes. The decision nodes (square node) represent the two competing interventions (control and PBMT groups), the chance nodes (circle node) represent the chances of occurrence of a specific outcome, and the terminal nodes (triangle node) depict the outcomes of the decision-making process.

Sensitivity analysis

Furthermore, a one-way sensitivity analysis was performed to verify the uncertainty of the parameters associated with PBMT, by varying one value in the model by a given amount and then examining the impact that the change has on the model's results. We tested the effects of both varying the costs and the effectiveness parameters of the model. Since POCP was similar in both groups, the variations in parameters were performed only for the PBMT group.

For the variation in cost of the dental staff, the variation of the average salary in Brazil, ranging from the highest (+ 28%) to lowest (− 12.9%) values was included. For the variation in drug prices, a ± 17% variation in the reference prices in the Drug Price List of the National Health Surveillance Agency of Brazil (ANVISA) was considered. For the variation in effectiveness regarding OM incidence, data from a systematic review by Oberoi et al. [17] were used, considering the 95% confidence interval limits of the relative risk of the incidence of severe OM in patients who underwent PBMT (RR = 0.37; 95%CI = 0.20–0.67). For the OHRQoL measurements, the interquartile range was applied—the first (Q25) and the third (Q75) quartiles were considered for the best and worst scenarios, respectively.

Statistical analysis

Pearson chi-square test for categorical variables was used to compare the clinical and demographic characteristics of the participants between groups, and to compare the OM severity scores (severe vs non-severe OM). The Mann-Whitney test was used to test between-group differences in OHRQoL scores between groups, and the Wilcoxon test was used to test within-group changes at the RT stages compared with baseline. Statistically significant differences were set when $p < 0.05$. All statistical analyses were performed using the IBM SPSS 20.0 statistical package (SPSS Inc., Chicago, IL, USA). Cost analyses, ICER calculation, and sensitivity analysis were performed using Microsoft Office Excel (Microsoft, Albuquerquer, NM, USA).

Results

A total of 71 participants who were recruited for the study were randomized to the two intervention groups. However, outcomes were analyzed for 48 patients who completed the follow-up in the PBMT group ($n = 25$) and the control group ($n = 23$). The detailed flowchart of the study, according to the CONSORT guidelines [26] for reporting of randomized clinical trials, is provided in Fig. 1. The clinical and pathological data are presented in Table 1.

Prevention of severe OM

Considering the prevention of new-onset severe OM (WHO scale) as a measure of treatment effectiveness, 16 patients of the PBMT group (64.0%) and 8 of the control group (34.8%) did not have severe OM. According to the NCI classification, 56% ($n = 14$) of the PBMT group and 26.1% ($n = 6$) of the control group did not have severe OM. NNT was 3.4 and 3.3

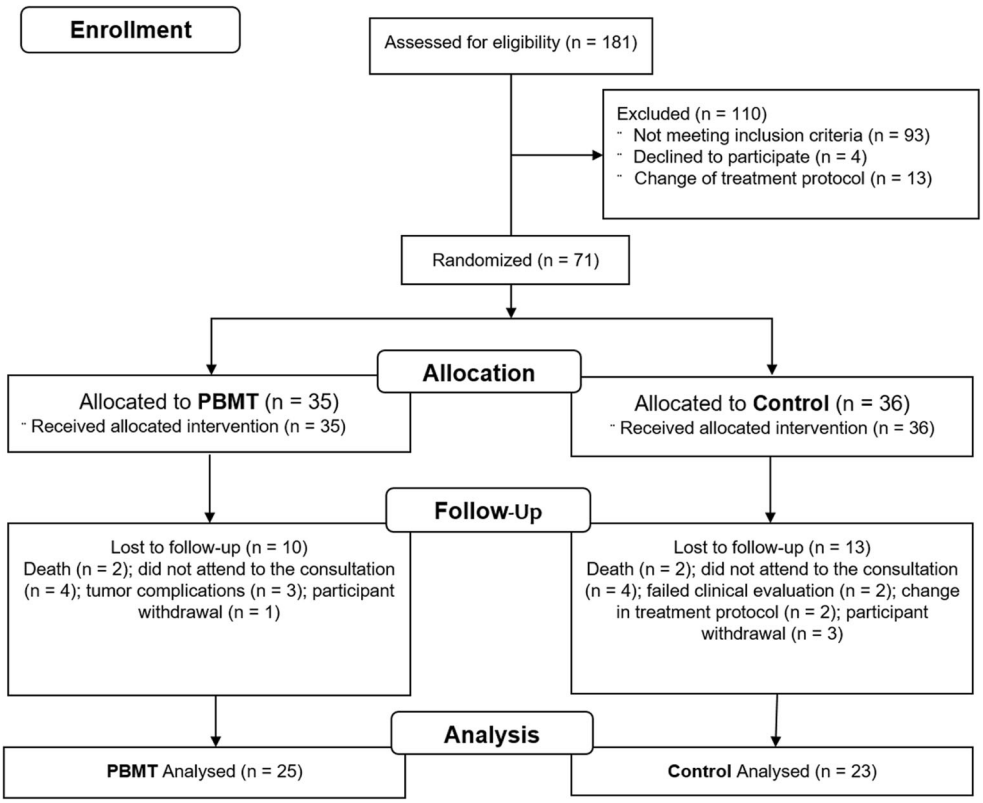

Fig. 1 Flowchart of the study

for WHO and NCI scales, respectively. No side effects or harms related to PBMT or POCP were observed. PMBT group presented lower incidences of severe OM compared with the control group at the 21st and 30th RT sessions for both the WHO and NCI scales (Fig. 2).

RT interruption

RT was interrupted due to severe OM for 2 (8%) patients in the PBMT group and 9 (39.1%) patients in the control group ($p = 0.010$). In the PBMT group, one interruption occurred in the second week (between the 7th and 14th RT sessions) and other in the third week (between the 21st and 30th RT sessions). In the control group, RT interruptions occurred in the second ($n = 2$), third ($n = 4$), and in the final week ($n = 2$) of the RT regimen. One patient had two RT interruptions in the first and last weeks.

Oral health-related quality of life

In the PBMT group, the OHIP-14 median score was 1.32 at the first appointment (0 RT) and increased to 3.78 in the 30th session ($p = 0.05$). While in the control group, median score at the first appointment (0 RT) was 0.49 and on the 30th was 9.76 ($p = 0.001$). Statistically significant difference was observed between the PBMT and control groups at the 30th RT session ($p = 0.006$).

The total variation of OHRQoL was 1.96 and 6.98 in the PBMT and control groups, respectively ($p = 0.01$).

Concerning the PROMS scale, there was a statistically significant difference ($p < 0.001$) in the PBMT group between baseline (median = 0) and final (median = 24) scores. In the control group, the baseline median PROMS score was 0, and it increased to 38.8 at the 30th RT session ($p < 0.001$). Although patients in the control group reported worse symptoms in the last evaluation, the difference did not reach statistical significance ($p = 0.06$).

The total variation in the OM patient-reported symptoms was 11 in the PBMT group and 38 in the control group ($p = 0.03$) (Supplementary Table 1).

Costs

The average cost of the laser equipment was $3349.75 with an EAC of $773.71. The cost related to the PBMT license was $1418.72. The items, services, and equipment used to calculate PBMT costs are presented in Supplementary Table 2.

To calculate the cost of one PBMT session, the average time of one PBMT session was 12.56 min/patient. Considering the fixed and variable costs, the cost of each PBMT session was $25.69. The cost of the entire therapy ranged from $774.50 to 1032.67. Each patient received approximately 35 PBMT sessions, resulting in an average cost of $900.16 per patient.

Table 1 Clinical and pathological data of participants (percent in parenthesis)

		Total *n* (%)	PBMT *n* (%)	Control *n* (%)	*p* value
Sex	Female	7 (14.6)	5 (20.0)	2 (8.7)	0.26
	Male	41 (85.4)	20 (80.0)	21 (91.3)	
Age in years—mean (SD)		59.75 ± 11.69	60.32 ± 9.76	59.13 ± 13.68	0.32
Location	Oral mucosa[a]	2 (4.2)	1 (4.0)	1 (4.3)	0.51
	Hard palate	1 (2.1)	-	1 (4.3)	
	Tongue	7 (14.6)	3 (12.0)	4 (17.4)	
	Floor of the mouth	2 (4.2)	1 (4.0)	1 (4.3)	
	Tongue base	26 (54.2)	16 (64.0)	10 (43.5)	
	Rhinopharynx	1 (2.1)	-	1 (4.3)	
	Hypopharynx	5 (10.4)	1 (4.0)	4 (17.4)	
	Glottis and supraglottis	4 (8.3)	3 (12.0)	1 (4.3)	
Size (T)	T1	2 (4.2)	1 (4.0)	1 (4.3)	0.79
	T2	10 (20.8)	5 (20.0)	5 (21.7)	
	T3	18 (37.5)	8 (32.0)	10 (43.5)	
	T4	18 (37.5)	11 (44.0)	7 (30.4)	
Nodal metastasis (N)	N0	23 (47.9)	10 (40.0)	13 (56.5)	0.22
	N1	6 (12.5)	2 (8.0)	4 (17.4)	
	N2	13 (27.1)	8 (32.0)	5 (21.7)	
	N3	6 (12.5)	5 (20.0)	1 (4.3)	
Distant metastasis (M)	M0	44 (91.7)	23 (92.0)	21 (91.3)	0.51
	M1	1 (2.1)	-	1 (4.3)	
	MX	3 (6.2)	2 (8%)	1 (4.3)	
Adjuvant CT[b]	Yes	6 (12.5)	3 (12.0)	3 (13.0)	0.56
	No	42 (87.5)	22 (88.0)	20 (87.0)	
Neoadjuvant CT	No	45 (93.8)	23 (92)	22 (95.7)	0.23
	DXT	1 (2.1)	-	1 (4.3)	
	TPF	2 (4.2)	2 (8.0)	-	
RT dose (Gy)—mean (SD)		63.88 (± 14.24)	66.88 (± 4.28)	60.61 (± 19.79)	0.13
RT type	2D	4 (8.3)	3 (12.0)	1 (4.3)	0.33
	3D	44 (91.7)	22 (88.0)	22 (95.7)	
Medications[c]	Antihypertensive	10 (25.6)	4 (20)	6 (31.6)	0.41
	Antidepressive	2 (5.1)	-	2 (10.5)	-
Multidisciplinary support team (yes)	Nutritionist	28 (58.3)	15 (60.0)	13 (56.5)	0.81
	Psychologist	19 (39.6)	9 (36.0)	10 (43.5)	0.77
	Speech therapist	6 (12.5)	1 (4.0)	5 (21.7)	0.06
	Physiotherapist	1 (2.1)	-	1 (4.3)	-
	Social worker	33 (68.8)	18 (72.0)	15 (65.2)	0.61
	Nurse	12 (25.0)	5 (20.0)	7 (30.4)	0.40

[a] Refers to buccal, labial mucosa, retromolar area, and vestibule

[b] The used drug was cisplatin (doses of 40 mg/m^2 for week scheme and 100 mg/m^2 for every 21 days)

[c] Refers to medications that may cause salivary flow rate change, information was available in 20 participants of PBMT group and 19 of control group

2D, bidimensional; *3D*, tridimensional; *CT*, chemotherapy; *DTX*, docetaxel (75 mg/m^2), cisplatin (75 mg/mg^2); *PBMT*, photobiomodulation therapy; *RT*, radiotherapy; *SD*, standard deviation; *TPF*, docetaxel (75 mg/m^2), 5-fluoracil (750 mg/m^2) and cisplatin (75 mg/m^2)

Additional interventions due to OM involved the use of nasoenteral tubes, opioids, NSAIDs, corticosteroids, electrolyte replacement agents, and polyvitamins. Only one patient in the control group required hospitalization. There was no difference between the groups regarding the number of patients requiring additional interventions ($p = 0.39$). Four patients (16%) from the PBMT group required complementary interventions due to OM, with an average cost of $27.44 PPP, ranging from $11.38 to $56.45. Six patients (26.1%) from the control group required additional interventions. The average cost of these interventions was $185.17 (range = $12.83–$745.08). Considering all patients from both groups,

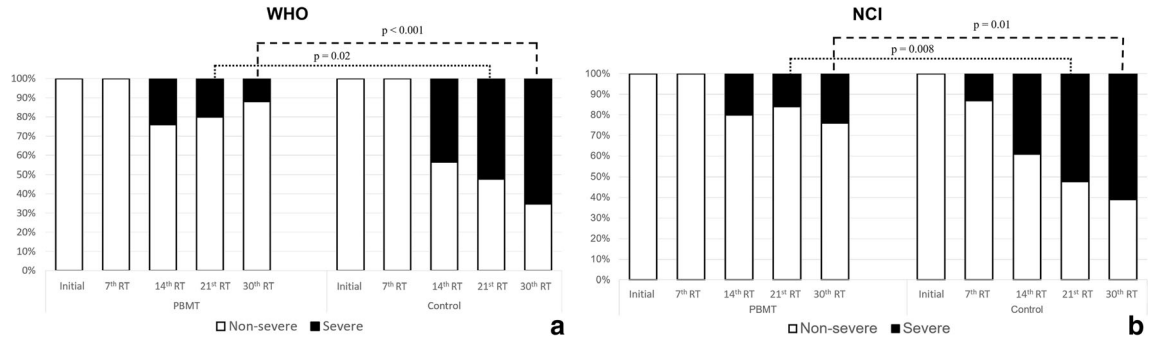

Fig. 2 Incidence of OM throughout the follow-up period. Connections between bars indicate statistically significant differences between groups (chi-square test). WHO: World Health Organization; NCI: National Cancer Institute; RT: Radiotherapy

the average cost was $905.65 and $48.30 in the PBMT and control groups, respectively. Thus, the incremental cost of using PBMT was $857.35 (Table 2).

Supplementary Figure 1 shows the decision tree diagram of the clinically relevant events, based on the WHO scale for the definition of occurrence of severe OM for the two interventions, as well as the course of action according to the need for additional interventions for each of the possible treatment outcomes.

Cost-effectiveness analysis

The cost-effectiveness analysis and ICER values for each measure of effectiveness are detailed in Table 3.

The sensitivity analysis was based on changing the cost and effectiveness measures to obtain a best and worst scenario for each of the study outcomes. For the best scenario, the number of severe OM cases in the PBMT group was considered to be 20% of the number of cases in the control group. A variation of − 17% and − 12.9% was taken into account in the medication and staff salary, respectively. For an interruption of treatment due to OM, the RR found was 0.20 (95% CI, 0.05–0.85); thus, in the best-case scenario, the number of interruptions of RT in the PBMT group was 5% of the value found in the control group. For OHRQoL measurements, Q25 of the variation found in the laser group was considered. For the OHIP-14 questionnaire, the variation in the best scenario was − 1.26 and 8.65 for the PROMS scale.

For the worst-case scenario, we consider that in the PBMT group the incidence of severe OM was 67% of the cases found in the control group. There was a variation of + 17% in the price of medicines and + 28% in the staff's salary. The number of interruptions avoided due to PBMT was considered to be 25% of those occurring in the control group. For the OHRQoL variation, the Q75 of the PBMT group were considered. Therefore, for the OHIP-14 questionnaire, the variation in the worst scenario was 4.97 and 32.6 for the PROMS scale.

Considering these changes in parameters, ICERs were calculated for the best (discounts) and worst (increases) scenarios, as described in Table 4.

Discussion

Despite the significant burden of OM in cancer treatment [13], only few studies explored the economic implications of

Table 2 Cost in $ PPP of interventions to treat oral mucositis

	n (%)		Mean ± SD	
	PBMT	Control	PBMT	Control
PBMT	-	-	900.16 ± 37.52	-
Visits to the emergency service	4 (16.0)	6 (26.1)	27.44 ± 17.93	185.17 ± 280.43
Nasoenteral tube	2 (8.0)	4 (17.4)	37.89 ± 18.32	36.25 ± 28.67
Opioids	2 (8.0)	4 (17.4)	0.25 ± 0.28	4.44 ± 6.73
NSAIDs	-	4 (17.4)	-	1.35 ± 1.37
Corticosteroids	2 (8.0)	5 (21.7)	0.19 ± 0.21	2.11 ± 3.25
Electrolyte replacement/polyvitamins	5 (20.0)	6 (26.1)	1.71 ± 1.86	15.63 ± 24.60
Hospitalization	-	1 (4.3%)	-	253.49
Final cost			905.65	48.30
PBMT incremental cost			857.35	

NSAIDs, nonsteroidal anti-inflammatory drugs; *PBMT*, photobiomodulation therapy; *SD*, standard deviation

Table 3 Cost-effectiveness analysis and the incremental cost-effectiveness ratios (ICERs) of the introduction of photobiomodulation therapy in the treatment of oral mucositis

	Outcome	Parameter	PBMT	Control	ICER	Interpretation
Cost ($PPP)		Incremental cost of PBMT	905.65	48.30	$ 857.35	Incremental cost of PBMT
Effectiveness	Incidence of OM (WHO scale)	% severe OM prevented	64%	34.8%	$ 2963.13	Cost to avoid one case of severe OM
	Incidence of OM (NCI scale)	% severe OM prevented	56%	26.1%	$ 2867.39	Cost to avoid one case of severe OM
	Incidence of RT interruption	% RT interruptions prevented	92%	60.9%	$ 2756.75	Cost to avoid one case of RT interruption
	OHIP-14 score	OHIP-14 variation	1.96	6.98	$ 170.79	Cost for 1-point reduction in OHIP-14 score
	PROMS score	PROMS variation	11	38	$ 31.75	Cost for 1-point reduction in PROMS score

PBMT, photobiomodulation group; *NCI*, National Cancer Institute; *OM*, oral mucositis; *RT*, radiotherapy; *WHO*, World Health Organization

treatments for mucositis [10, 14, 27]. Bezinelli et al. [10] showed that Brazilian patients undergoing stem cell transplantation who underwent PBMT for OM control had 30% lower hospital costs compared with patients who received only oral care instructions. These findings corroborate our study results, in which we identified that the hospital costs of the PBMT group, excluding the cost of PBMT, were lower than those of the control group.

Antunes et al. [14] investigated the cost-effectiveness of PBMT in the treatment of OM due to radiochemotherapy from the perspective of the Brazilian Public Health System. The estimated cost for a PBMT session was US$41.18, and the incremental cost was US$1689.00 per patient. The calculated ICER was US$4961.37 to avoid one case of severe OM [14]. In our study, the estimated cost per session was $25.69 PPP and the incremental cost of PBMT was $857.35 PPP, and the ICER found was $2936.13 PPP and $2867.39 PPP to avoid one case of severe OM, according to the WHO and NCI scales, respectively.

In their study, Antunes et al. [14] calculated the cost related to the implementation of a dental care center for cancer patients. Whereas in our study, these costs were not included, because we assumed that, regardless of the treatment administered (PBMT or POCP), they are similar. In addition, the dental staff considered a great number of professionals in the study previously cited [14] and all events resulted from OM derived from secondary data. However, our results corroborate with the findings by Antunes et al. [14], who suggested that the costs due to OM were lower in patients undergoing PBMT and that this therapy is more cost-effective than the standard approach.

Another promising finding of our study was ICER to prevent an interruption in RT due to OM, which was of $2756.75. It is important to note that unintentional interruptions in cancer treatment are associated with lower survival rates and locoregional control [28–30]. To date, there are no similar studies that can be compared with the findings of our study.

Our results showed that the ICERs, to prevent a 1-point reduction in OHRQoL, were $170.79 for the OHIP-14 instrument, and $31.75 for the PROMS scale. These findings suggest that PBMT is cost-effective for reducing both severe OM and preventing OHRQoL negative impacts. This also is the first study to assess the ICER of PBMT considering patient-reported outcomes. Since the most common instrument used for cost-utility analysis may not be suitable to measure OHRQoL [31, 32], we did not measure the quality-adjusted life years (QALY). However, the use of OHIP-14 scores as a parameter of effectiveness, and as health state values, has been described in other studies [31, 32], especially in patients to whom QALY cannot be measured [33].

Table 4 ICER considering the best and worst-case scenario

	Base-case	Best scenario	Worst scenario
Prevention of severe OM (WHO scale)	$ 2936.13	$ 1398.55	$ 4315.94
Prevention of severe OM (NCI scale)	$ 2867.39	$ 2339.71	$ 4367.93
RT Interruption	$ 2756.75	$ 2002.77	$ 18,484.89
OHIP-14	$ 170.79	$ 90.29	$ 541.10
PROMS	$ 31.75	$ 25.35	$ 201.41

OM, oral mucositis; *WHO*, World Health Organization; *NCI*, National Cancer Institute; *RT*, radiotherapy; *ICER*, incremental cost-effectiveness ratio

There are no previous economic studies of other therapies adopted for OM in patients undergoing HNC treatment. Nooka et al. [27] showed that the ICER of palifermin to avoid 1 day of intravenous narcotic analgesics (the use of this drug was associated with severe OM) in patients undergoing hematopoietic stem cell transplantation was US$5500 for patients with myeloma and US$14,000 for patients with lymphoma. Palifermin was able to reduce the costs associated with these hematopoietic cancers [27]. This drug may be effective in preventing severe OM in patients with HNC treated with RT associated with CT [34]. However, further studies on the effectiveness and cost of palifermin are needed to allow comparisons between this drug and PBMT.

It is important to note that, before initiating RT, participants of this study were submitted to a comprehensive assessment of dental and oral conditions, as well as the control of all local problems that could affect patient outcomes during the course of the longitudinal assessments. After that, during the RT treatment regimen, the participants were rigorously monitored in order to preserve a satisfactory oral health. This means that all participants were submitted to the Preventive Oral Care Program [18, 35].

A limitation of our study was the fact that the patient's follow-up was interrupted when RT was discontinued. Typically, this occurred because most of the study participants were originally from the state countryside or small cities of the state, and most of them preferred to stay at home to recover from OM during the treatment interruption. We believe that this could have influenced the costs of treating severe OM because rather than visiting the hospital's emergency department, patients either attended an emergency service at their hometown or did not attend at all. Additionally, this study was based on the hospital costs, and the costs of ambulatory treatment of OM, such as the use of NSAIDs, were not considered due to the difficulty of gathering this information. Therefore, the costs for the public health system may be higher than the overall costs described in our study.

Recent guidelines for prevention of OM in patients undergoing RT [36] describe the use of red laser at 660 nm, with an energy per point of 3 J and laser application less than 1 cm of the tissue [37]. For patients undergoing RT associated with CT, the use of the protocol described by Antunes et al. [38] and Oton-Leite et al. [39] was recommended. The protocol used in our study was similar to that used by Oton-Leite et al. [39], except for the weekly frequency of the PBMT. In our study, PBMT was administered 5 times a week, whereas Oton-Leite et al. performed PBMT 3 times a week. Thus, we believe cost-effectiveness studies must be conducted, especially considering the protocols previously described.

The relevance of our study lies especially within the context of the public health systems, as it strengthens the scientific evidence toward implementing PBMT as a new technology to treat adverse effects of HNC treatment. Although our study was conducted from the providers' perspective, the hospital in which the study was performed is a private philanthropic institution with 80% of the patient treatments funded by the public health system. Therefore, we believe that the results can be extrapolated to public health hospitals. Our results contribute to provide evidence for the incorporation of PBMT in the list of procedures available in both public and private hospital care.

Conclusion

Our results favor the incorporation of PBMT as a therapy to prevent and treat severe OM associated to HNC treatment, in public and private hospitals. PBMT was a more cost-effective option than standard oral care measures alone in preventing severe degrees of OM, reducing OHRQoL impacts, and interruption of RT protocol.

Author contributions and consent for publication All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Allisson Filipe Lopes Martins, Marília Oliveira Morais, Sebastião Silvério Sousa-Neto, Angélica Ferreira Oton-Leite, and Tulio Eduardo Nogueira. The methods of the study were designed by Allisson Filipe Lopes Martins, Marize Campos Valadares, Nilcena Maya Aires Freitas, Cláudio Rodrigues Leles, and Elismauro Francisco de Mendonça. The first draft of the manuscript was written by Allisson Filipe Lopes Martins and Tulio Eduardo Nogueira. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding information We thank the Foundation for Research Support in the State of Goiás—FAPEG/Ministry of Health of Brazil/ Brazilian National Council for Scientific and Technological Development—CNPq (PPSUS–201710267001233), and the Brazilian National Council for Scientific and Technological Development—CNPq (307906-7) for funding this study. This funding source did not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Compliance with ethical standards

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

Ethics approval This research was approved by the Ethics Research Committee of Universidade Federal de Goiás (Protocol 2.053.687/2017) and the Araujo Jorge Cancer Hospital (Protocol 2.131.323/2017).

Consent to participate All participants signed an informed consent to participate of this study.

References

1. Barasch A, Peterson DE (2003) Risk factors for ulcerative oral mucositis in cancer patients: unanswered questions. Oral Oncol 39(2):91–100

2. Khouri VY, Stracieri AB, Rodrigues MC, Moraes DA, Pieroni F, Simões BP et al (2009) Use of therapeutic laser for prevention and treatment of oral mucositis. Braz Dent J 20(3):215–220
3. Pico JL, Avila-Garavito A, Naccache P (1998) Mucositis: its occurrence, consequences, and treatment in the oncology setting. Oncologist 3(6):446–451
4. Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M et al (2004) Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer 100(9Suppl):1995–2025
5. Sonis ST (2011) Oral mucositis. Anti-Cancer Drugs 22(7):607–612
6. Elting LS, Cooksley CD, Chambers MS, Garden AS (2007) Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies. Int J Radiat Oncol Biol Phys 68(4):1110–1120
7. Bese NS, Hendry J, Jeremic B (2007) Effects of prolongation of overall treatment time due to unplanned interruptions during radiotherapy of different tumor sites and practical methods for compensation. Int J Radiat Oncol Biol Phys 68(3):654–661
8. Russo G, Haddad R, Posner M, Machtay M (2008) Radiation treatment breaks and ulcerative mucositis in head and neck cancer. Oncologist. 13(8):886–998
9. Nonzee NJ, Dandade NA, Patel U, Markossian T, Agulnik M, Argiris Aet al. (2008) Evaluating the supportive care costs of severe radiochemotherapy-induced mucositis and pharyngitis: results from a Northwestern University costs of cancer program pilot study with head and neck and nonsmall cell lung cancer patients who received care at a county hospital, a Veterans Administration hospital, or a comprehensive cancer care center. Cancer. 113(6):1446–1452
10. Bezinelli LM, de Paula EF, da Graça Lopes RM, Biazevic MG, de Paula EC, Correa L et al (2014) Cost-effectiveness of the introduction of specialized oral care with laser therapy in hematopoietic stem cell transplantation. Hematol Oncol 32(1):31–39
11. Oton-Leite AF, Elias LS, Morais MO, Pinezi JC, Leles CR, Silva MA et al (2013) Effect of low-level laser therapy in the reduction of oral complications in patients with cancer of the head and neck submitted to radiotherapy. Spec Care Dentist 33(6):294–300
12. Oton-Leite AF, Corrêa de Castro AC, Morais MO, Pinezi JC, Leles CR, Mendonça EF (2012) Effect of intraoral low-level laser therapy on quality of life of patients with head and neck cancer undergoing radiotherapy. Head Neck 34(3):398–404
13. Berger K (2018) Burden of oral mucositis: a systematic review and implications for future research. Oncol Res Treat 41(6):399–405
14. Antunes HS, Schluckebier LF, Herchenhorn D, Small IA, Araújo CM, Viégas CM et al (2016) Cost-effectiveness of low-level laser therapy (LLLT) in head and neck cancer patients receiving concurrent chemoradiation. Oral Oncol 52:85–90
15. Zadik Y (2019) Photobiomodulation for the palliation of oral mucositis in cancer patients: the future is here. Future Oncol 15(32): 3647
16. Martins AFL, Nogueira TE, Morais MO, Oton-Leite AF, Valadares MC, Batista AC, Freitas NMA, Leles CR, Mendonça EF (2019) Effect of photobiomodulation on the severity of oral mucositis and molecular changes in head and neck cancer patients undergoing radiotherapy: a study protocol for a cost-effectiveness randomized clinical trial. Trials. 20(1):97
17. Oberoi S, Zamperlini-Netto G, Beyene J, Treister NS, Sung L (2014) Effect of prophylactic low-level laser therapy on oral mucositis: a systematic review and meta-analysis. PLoS One 9(9): 2107418
18. Morais MO, Martins AFL, Jesus APG, Sousa-Neto SS, Costa AWF, Pereira CH et al (2020) A prospective study on oral adverse effects in head and neck cancer patients submitted to a preventive oral care protocol. Support Care Cancer:2020. https://doi.org/10.1007/s00520-019-05283-1
19. Parulekar W, Mackenzie R, Bjarnason G, Jordan RC (1998) Scoring oral mucositis. Oral Oncol 34(3):63–71
20. National Cancer Institute (NCI), National Cancer Health (NIH), Common Toxicity Criteria (CTCAE) (2017) Version 5.0. https://ctep.cancer.gov. Accessed 25 Jan 2019
21. Pires CP, Ferraz MB, de Abreu MH (2006) Translation into Brazilian Portoguese, cultural adaptation and validation of the Oral Health Impact Profile (OHIP-49). Braz Oral Res 20(3):263–268
22. Oliveira BH, Nadanovsky P (2005) Psychometric properties of the Brazilian version of the Oral Health Impact Profile-short form. Community Dent Oral Epidemiol 33(4):307–314
23. Bezinelli LM, Eduardo FP, Neves VD, Correa L, Lopes RM, Michel-Crosato E et al (2016) Quality of life related to oral mucositis of patients undergoing haematopoietic stem cell transplantation and receiving specialised oral care with low-level laser therapy: a prospective observational study. Eur J Cancer Care 25(4):668–674
24. Turner HC, Lauer JA, Tran BX, Teerawattananon Y, Jit M (2019) Adjusting for inflation and currency changes within health economic studies. Value Health 22(9):1026–1032
25. OECD (2020) Exchange rates (indicator). doi: https://doi.org/10.1787/037ed317-en (Accessed on 02 February 2020)
26. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG, Consolidated Standards of Reporting Trials Group (2010) CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol 63(8):e1–e37
27. Nooka AK, Johnson HR, Kaufman JL, Flowers CR, Langston A, Steuer C, Graiser M, Ali Z, Shah NN, Rangaraju S, Nickleach D, Gao J, Lonial S, Waller EK (2014) Pharmacoeconomic analysis of palifermin to prevent mucositis among patients undergoing autologous hematopoietic stem cell transplantation. Biol Blood Marrow Transplant 20(6):852–857
28. Russo G, Haddad R, Posner M, Machtay M (2008) Radiation treatment breaks and ulcerative mucositis in head and neck cancer. Oncologist. 13(8):886–898
29. Thomas K, Martin T, Gao A, Ahn C, Wilhelm H, Schwartz DL (2017) Interruptions of head and neck radiotherapy across insured and indigent patient populations. J Oncol Pract 13(4):e319–e328
30. Lazarev S, Gupta V, Ghiassi-Nejad Z, Miles B, Scarborough B, Misiukiewicz KJ et al (2017) Premature discontinuation of curative radiation therapy: insights from head and neck irradiation. Adv Radiat Oncol 23(3):62–69
31. Hulme C, Yu G, Browne C, O'Dwyer J, Craddock H, Brown S et al (2014) Cost-effectiveness of silicone and alginate impressions for complete dentures. J Dent 42(8):902–907
32. Hulme C, Robinson PG, Saloniki EC, Vinall-Collier K, Baxter PD, Douglas G, Gibson B, Godson JH, Meads D, Pavitt SH (2016) Shaping dental contract reform: a clinical and cost-effective analysis of incentive-driven commissioning for improved oral health in primary dental care. BMJ Open 6(9):e013549
33. Brennan DS, Spencer AJ (2006) Mapping oral health related quality of life to generic health state values. BMC Health Serv Res 6:96
34. Riley P, Glenny AM, Worthington HV, Littlewood A, Fernandez Mauleffinch LM, Clarkson JE et al (2017) Interventions for preventing oral mucositis in patients with cancer receiving treatment: cytokines and growth factors. Cochrane Database Syst Rev 11:CD011990
35. Morais MO, Elias MRA, Leles CR, Pinezi JCD, Mendonça EF (2016) The effect of preventive oral care on treatment outcomes of a cohort of oral cancer patients. Support Care Cancer 24(4): 1663–1670
36. Zadik Y, Arany PR, Fregnani ER, Bossi P, Antunes HS, Bensadoun RJ et al (2019) Systematic review of photobiomodulation for the

management of oral mucositis in cancer patients and clinical practice guidelines. Support Care Cancer 27(10):3969–3983

37. Gautam AP, Fernandes DJ, Vidyasagar MS, Maiya AG, Guddattu V (2015) Low level laser therapy against radiation induced oral mucositis in elderly head and neck cancer patients-a randomized placebo controlled trial. J Photochem Photobiol B 144:51–56
38. Antunes HS, Herchenhorn D, Small IA, Araújo CMM, Viégas CMP, Cabral E, Rampini MP, Rodrigues PC, Silva TGP, Ferreira EMS, Dias FL, Ferreira CG (2013) Phase III trial of low-level laser therapy to prevent oral mucositis in head and neck cancer patients treated with concurrent chemoradiation. Radiother Oncol 109(2): 297–302
39. Oton-Leite AF, Silva GB, Morais MO, Silva TA, Leles CR, Valadares MC et al (2015) Effect of low-level laser therapy on chemoradiotherapy-induced oral mucositis and salivary inflammatory mediators in head and neck cancer patients. Lasers Surg Med 47(4):296–305