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Randomised Controlled Trial
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# Photobiomodulation with low-level laser therapy reduces oral mucositis caused by head and neck radio-chemotherapy: prospective randomized controlled trial

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*Abstract.* The objective of this study was to assess the effectiveness of photobiomodulation with low-level laser therapy (LLLT) as a preventive and therapeutic procedure for the treatment of oral and oropharyngeal mucositis caused by radio-chemotherapy in patients diagnosed with oral squamous cell carcinoma (SCC). An experimental, prospective, double-blind, randomized controlled study was conducted involving patients diagnosed with oral SCC undergoing oncological treatment. The variables analyzed included grade, appearance, and remission of mucositis. A final sample of 26 patients was included: 11 (42.3%) in the study group and 15 (57.7%) in the control group; their average age was 60.89 ± 9.99 years. Statistically significant differences between the groups were observed from week 5 of oncological treatment; 72.7% of the laser group showed normal mucosa (mucositis grade 0), while in the control group, 20.0% showed grade 0 mucositis and 40.0% showed grade 2 mucositis ($P < 0.01$). No statistically significant difference between the groups was found regarding the application or use of medication throughout the study period ($P > 0.05$). The tolerance evaluation did not show any statistically significant difference between the groups regarding the occurrence of side effects or adverse events during the trial ($P > 0.05$). Photobiomodulation with LLLT reduces the incidence and severity of mucositis in patients treated with radiotherapy ± chemotherapy.

Key words: oral squamous cell carcinoma cancer; oral mucositis; photobiomodulation; low-level laser therapy.

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Combination therapy involving radiotherapy and chemotherapy has proven to be an effective alternative for the treatment of head and neck malignant tumours in terms of survival and recovery when compared with radiotherapy alone[1]. On occasion, this combined treatment may be hampered and limited by oral mucositis, a severe and frequent complication that requires that oncological treatment be stopped temporarily or even permanently[2].

Oral mucositis is a result of direct irradiation or chemotherapy leading to a series of inflammatory changes initially observed as erythematous changes in the epithelial mucosa. These changes can turn into ulcerative lesions that expose the submucosa when they become severe[3]. The incidence rate of oral mucositis is approximately 85–100%, varying slightly depending on the oncological regimen used[4]. The resulting lesions are usually found in non-keratinized mucosa such as the ventral and lateral surface of the tongue, the buccal and labial mucosa, the floor of the mouth, and the soft palate[5].

Strategies for reducing the incidence of oral mucositis in oncological patients have yet to be clearly defined. Many published articles have emphasized the importance of preventing mucositis through intensive oral care and thorough hygiene practices. While there is still no standardized protocol, many authors have found that photobiomodulation provides better palliative results[6–9].

Low-level laser therapy (LLLT) emissions fall within the near-infrared or red infrared spectrum region (632, 670, and 830 nm). With an average power density of between 5 and 150 mW/cm$^2$, the laser does not produce any thermal effects, as the power used is lower and the applicable area is larger; therefore, the heat disperses and produces a biostimulating effect within the cells, as well as analgesic and anti-inflammatory effects. These beneficial effects are caused by an increase in cellular trophism and microvascular density within the local connective tissue, accelerating wound healing and reducing post-operative swelling[10–12].

The objective of this study was to assess the effectiveness of photobiomodulation with LLLT when compared to a control group, as a preventive and therapeutic procedure for the treatment of cases of oral mucositis triggered by radiotherapy and chemotherapy in patients diagnosed with squamous cell carcinoma (SCC) of the oral cavity and oropharynx and treated with radio-chemotherapy.

## Materials and methods

### Study protocol

This experimental, prospective, double-blind, randomized controlled study was performed on patients diagnosed with primary oral and oropharyngeal SCC receiving oncological treatment at the Department of Radiation Oncology of Virgen del Rocío University Hospital. The study was approved by the Ethics Committee of Virgen del Rocío University Hospital and was conducted in accordance with the Declaration of Helsinki. Patients voluntarily agreed to participate after being informed of the objectives, benefits, identified risks and complications, possible alternatives, and assumed rights and responsibilities. The CONSORT guidelines were followed for the evaluation of this clinical study (**Supplementary Material**, File 1).

### Inclusion criteria

The inclusion criteria were patients aged 18–65 years, previously diagnosed with oral or oropharyngeal SCC, and receiving a combined treatment of radiotherapy for 7 weeks (conventional fractionation reaching 70 Gy in the tumour and affected lymph nodes, at 2 Gy per day excluding weekends) and chemotherapy on days 1, 22, and 43 of irradiation (cisplatin 100 mg/m$^2$ intravenous on days 1, 22, and 43 of irradiation, or cetuximab 400 mg/m$^2$ as a single loading dose prior (1 week before) to treatment with radiotherapy and 250 mg/m$^2$ weekly during radiotherapy (eight cycles in total)). All patients had to present an ECOG stage of 0–1 (Eastern Cooperative Oncology Group)[13].

All patient cases were initially reviewed by a multidisciplinary tumour committee, in which the therapeutic approach for each patient was decided according to their staging and severity. Patients undergoing chemotherapy and radical radiotherapy treatment were those who were not suitable for surgery from the beginning. Patients undergoing adjuvant chemotherapy and radiotherapy were those who had positive tumour resection margins or extracapsular nodal spread.

### Exclusion criteria

The exclusion criteria were patients with a hypersensitivity or allergy to one of the components included in the study, patients with HIV, diabetes, or an autoimmune disease, and patients who did not meet the aforementioned inclusion criteria.

### Oral and general assessments

Before starting oncological treatment, the patients were evaluated for the presence of risk factors for oral complications through a complete oral and dental check-up, which included a radiographic examination[14]. An intensive oral care protocol based on the treatment of dental lesions prior to radio-chemotherapy was also conducted, and patients were given comprehensive instructions on maintaining proper oral hygiene. Patients were warned of the importance of avoiding contraindicated drugs or procedures, such as the simultaneous use of mouthwashes or topical drugs not already taken into account in the study.

One week prior to oncological treatment, an identical protocol for the prevention and treatment of mucositis was developed for all patients, with the exception of the application of the variable under study (LLLT).

### Photobiomodulation protocol

A diode laser (ezlase; BIOLASE, Irvine, CA, USA) with a wavelength of 940 nm was used for both groups. In the study group, the laser was applied on the mucosa, perpendicular to the irradiated surface. The power used was 0.5 W with an energy density of 0.5 J/s. The irradiation time was 6 seconds per point using a beam diameter of 0.036 cm$^2$ (wavelength 940 nm, 0.5 W continuous wave laser, illuminated area 0.036 cm$^2$, irradiance 13.88 W/cm$^2$, irradiation time 360 seconds, energy 180 J, energy density 83.3 J/cm$^2$). The irradiations were performed intraorally, avoiding the area of the tumour. The laser was applied at a total of 72 identified points in this study: 12 points were on the buccal mucosa (right and left), eight on the mucosa of the upper and lower lip, 12 on the hard palate, four on the soft palate, 12 on the lingual surface of the tongue, 10 on the left and right lateral edges of the tongue, eight on the ventral surface of the tongue, four on the floor of the mouth, and one on each labial commissure. In the control group, the same procedure was simulated with the laser turned off.

Patients in both groups were blinded to the procedure by placing a mask covering their eyes. The doctor who applied the laser was not blinded to whether the laser was off or not. However, the mucosal evaluator was blinded to the use of the laser; the evaluator was a different person to the one applying the laser (either effectively or placebo) (FMC or MASF applied the laser; JPI was the evaluator). The

evaluator did not know to which group the patients had been assigned. The application of the laser (placebo or effective) was performed in a room and building different from the place where the evaluations were made within the Virgen del Rocío Hospital complex. Therefore, the double-blinding applies to the patient and the evaluator.

This protocol was maintained throughout the entire process and was continued for 3 weeks after the completion of the oncological treatment. Values were therefore obtained at 12 visits, with this treatment only coinciding with the visits between the second visit (start of radiotherapy treatment) and the ninth visit (end of radiotherapy treatment).

### Clinical parameters and follow-up

The variables analyzed included grade, appearance, and remission of mucositis, daily use and/or application of analgesic drugs, infectious complications, and treatment tolerance. In addition to the outcomes of therapy, any clinical evidence of new potentially malignant or malignant lesions in the oral cavity or within regional sites were recorded, as well as the rate of recurrence (local/regional and distant relapse rates) or any new (second) primary tumours; however, these were not included in the analysis between groups. Overall survival (OS) was defined as the period between random assignment to either the treatment or placebo group and death. Disease-free survival (DFS) was also evaluated. This was defined as the period between the date of complete response to treatment and treatment ending and first relapse, defined as a relapse of local or regional disease (primary site or regional lymph node disease), or the presence of distant metastasis, or death.

### Oral mucositis assessments

Initial examinations of the oral mucosa were documented prior to the commencement of radio-chemotherapy (1 week before), during the next weekly check-ups, and three weeks after completing oncological treatment (12 visits in total). The objective was to determine the times of onset and complete remission of mucositis. The data collected were added to the patients' medical records. The integrity of the mucosa was evaluated for each patient using the scale developed by the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC)[15] (Table 1), which establishes five grades of mucositis according to the severity of the lesion. The scale ranges from 'no change from the baseline situation' (grade 0) to 'ulceration and/or necrosis' (grade 4).

*Table 1.* Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) scale for oral mucositis.

| | |
|---|---|
| Grade 0 | No change from baseline |
| Grade 1 | Erythema; patient may experience mild pain not requiring analgesic |
| Grade 2 | Patchy mucositis that may produce an inflammatory serosanguineous discharge; patient may experience moderate pain |
| Grade 3 | Confluent fibrinous mucositis; may include severe pain requiring narcotic |
| Grade 4 | Ulceration, haemorrhage, or necrosis |

Patients received a booklet in which they logged whether they had used any analgesic or anti-inflammatory medications for mucositis, specifying the quantity of medication required daily. The onset of complications caused by superinfection of the mucositis lesions was evaluated according to the patient's clinical manifestations and the appearance of the ulcerations (colouration, presence of purulent exudate, and foul odour). This evaluation was performed before the start of chemo-radiotherapy, during the next weekly check-ups, and three weeks after the completion of the patient's oncological treatment.

Tolerance was evaluated based on the frequency with which patients showed at least one adverse effect during the trial, with the nature and description of the adverse effect also being indicated.

To avoid discrepancies between examiners, the same blinded examiner recorded all studied variables during the examinations, while a different clinician conducted the LLLT (study group) and its simulation (control group).

### Statistical analysis

The sample size was calculated taking into account the mean difference of weeks with mucositis expected between the patients in the study group and those in the control group, to identify a difference of 2 weeks, assuming a standard deviation of 2. A unilateral test, with a confidence level of 95% and statistical power of 80%, was designated, to obtain a minimum sample size adjusted to losses of 12 persons per group. Considering a loss of up to 50% in each group, given the follow-up time, the inclusion of 18 patients per group was estimated. Patients were assigned randomly to either the study or the control group using random allocation software.

The statistical analysis was performed using IBM SPSS Statistics version 19.0 (IBM Corp., Armonk, NY, USA) at the Research Department of Virgen del Rocío University Hospital. The $\chi^2$ test was used to analyze the data obtained in the comparison of qualitative variables, and the Student *t*-test was used to compare mean values, after confirming the normality of the data with the Kolmogorov–Smirnov test.

To minimize biases within the questionnaires and their design, interviews and examinations were adapted using the following precautions: only previously validated and tested questionnaires were used, formal written instructions were provided to interviewers, and these interviewers underwent careful training prior to commencing the interviews.

## Results

The initial sample comprised 36 patients of both sexes aged between 18 and 65 years treated between 2013 and 2015. However, only 26 patients completed the full follow-up period; thus the final sample in this study was 26 patients. Eleven patients were assigned to the LLLT group (42.3%) and 15 patients to the control group (57.7%) (Fig. 1).

Clinical and pathological characteristics of the patients, the treatment modalities used, and the survival outcomes are shown in Table 2. The average age of the total sample was 60.89 ± 9.99 years. The average age of the participants in the study group was 61.01 ± 9.22 years, and in the control group was 60.13 ± 10.77 years. In terms of sex distribution, a total of 20 men and six women were included in the study, resulting in a statistically significant difference in the participation of men and women in the study and control groups ($P < 0.05$). The study group included 11 men and no women, while the control group included nine men and six women. No significant differences were found in the classification of the cancer according to stage, or in the histological differentiation, patient tobacco use, or oncological treatment used. The sites of primary appearance of the tumour are also shown in Table 2.

The researchers analyzed the number of weeks the patients participated in the study and the number of weeks in which

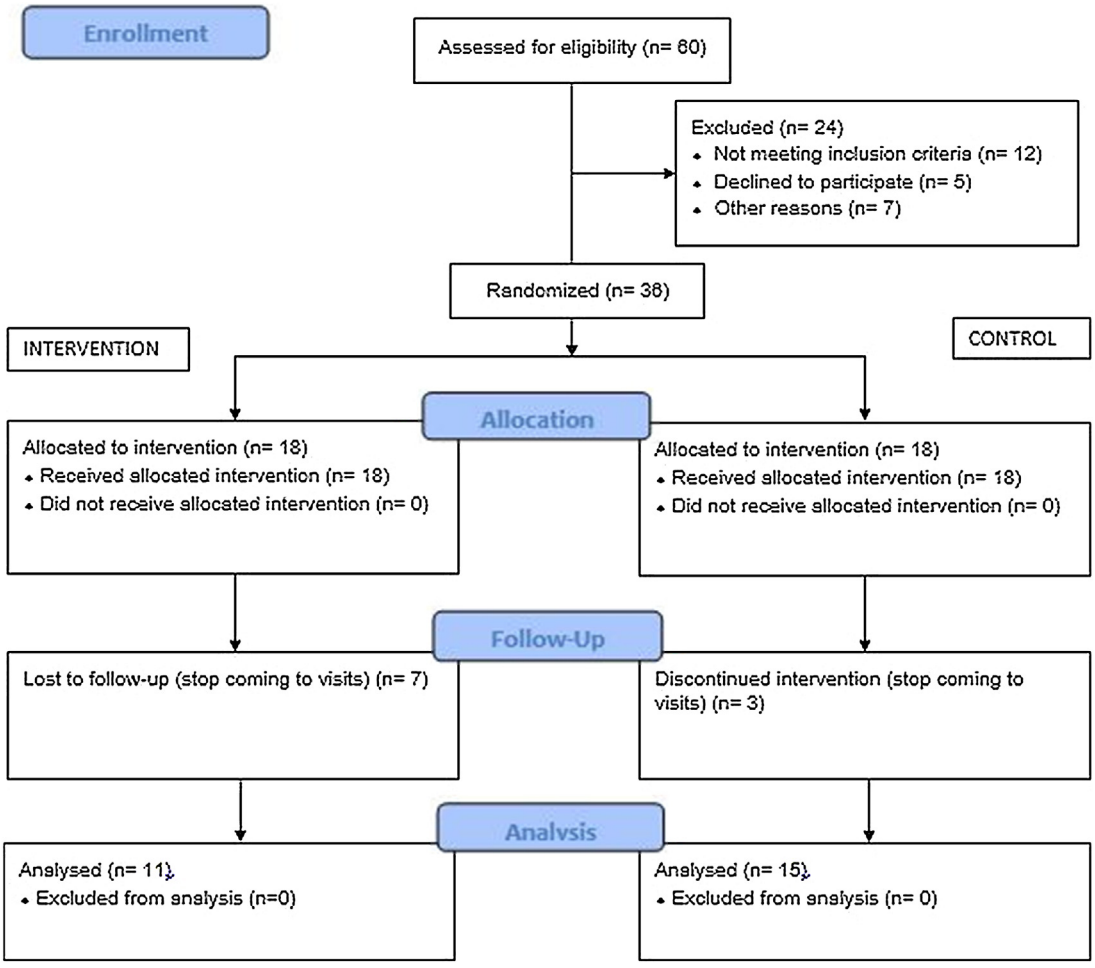


*Fig. 1.* Flowchart of the patients analyzed in the study.

the patients presented mucositis according to the RTOG/EORTC scale (Table 3). Statistically significant differences were observed between the groups beginning at week 5 of oncological treatment: 72.7% of the patients in the laser group showed a normal mucosa (grade 0), while in the control group, 20.0% of the patients showed grade 0 mucositis and 40% showed grade 2 mucositis; this difference was statistically significant ($P < 0.01$). Furthermore, during weeks 7 and 8, no grade 3 mucositis was found in the laser group; however, 33.3% (week 7) and 46.2% (week 8) of the patients in the control group showed confluent mucositis (**Supplementary Material**, File 2).

No statistically significant differences were found between the study and control groups with regard to the application or use of medication throughout the study period ($P > 0.05$).

A total of 13 patients suffered infectious complications in the oral cavity, with a statistically significant difference between the groups. Only two patients in the study group presented infectious complications, while 11 patients in the control group presented infectious complications ($P < 0.01$).

The tolerance evaluation did not show any statistically significant differences between the study and control group with regard to the occurrence of side effects or adverse events during the trial ($P > 0.05$).

Results were thoroughly cross-referenced regarding the sex variable to determine whether the differences between the study and the control groups may have been due to sex rather than type of treatment. No significant differences were observed, and in general, the few differences observed indicated a lower level of deterioration in women, which did not decrease the relevance of the laser.

## Discussion

Nowadays, the treatment of the advanced stages of oral SCC is based on the application of programmed concurrent sessions of chemoradiotherapy (CRT), and oral mucositis is the most frequent acute inflammatory reaction caused by radiotherapy and/or chemotherapy treatment[16]. In a typical radiotherapy treatment regimen, the first radiation dose (10–20 Gy) results in hyperkeratinization of the oral mucosa. This is clinically visible as a slight discoloration that frequently goes undetected. Once 20 Gy has been exceeded, erythema begins to appear — the first clinical sign of mucositis. The most severe stage appears above 30 Gy of total accumulated dose, often after the third week of treatment: ulcerations may appear covered by a pseudomembrane, which favours bacterial colonization and increases the risk of superinfection. Once radiotherapy treatment has been completed, the mucositis generally subsides within a period of 2–6 weeks[16].

Oral mucositis has a severe impact on oral functions, compromising the patient's general health[17]. Its frequency and severi-

*Table 2*. General variables studied in the sample[a].

| Studied variables | Total sample Frequency (%) | Laser group Frequency (%) | Control group Frequency (%) |
|---|---|---|---|
| Sex | | | |
| Male | 20 (76.9) | 11 (100.0)* | 9 (60.0)* |
| Female | 6 (23.1) | 0 (0.0)* | 6 (40.0)* |
| Location | | | |
| Floor of mouth | 5 (19.2) | 3 (27.3) | 2 (13.3) |
| Oropharynx | 10 (38.5) | 4 (36.4) | 6 (40.0) |
| Tongue | 6 (23.1) | 1 (9.1) | 5 (33.3) |
| Alveolar ridge | 3 (11.5) | 2 (18.2) | 1 (6.7) |
| Retromolar trigone | 2 (7.7) | 1 (9.1) | 1 (6.7) |
| Cancer stage[b] | | | |
| Stage I | 1 (4.2) | 0 (0.0) | 1 (7.7) |
| Stage II | 5 (20.8) | 2 (18.2) | 3 (23.1) |
| Stage III | 7 (29.2) | 3 (27.3) | 4 (30.8) |
| Stage IV | 11 (45.8) | 6 (54.5) | 5 (38.5) |
| Histological differentiation[c] | | | |
| Well-differentiated | 6 (26.1) | 1 (10.0) | 5 (38.5) |
| Moderately differentiated | 11 (47.8) | 6 (60.0) | 5 (38.5) |
| Poorly differentiated | 6 (26.1) | 3 (30.0) | 3 (23.1) |
| Tobacco use | | | |
| Yes | 8 (30.8) | 2 (18.2) | 6 (40.0) |
| No | 4 (15.4) | 3 (27.3) | 1 (6.7) |
| Former smoker | 14 (53.8) | 6 (54.5) | 8 (53.3) |
| Oncology treatment | | | |
| RT | 3 (11.5) | 2 (18.2) | 1 (6.7) |
| CT + RT | 12 (46.2) | 6 (54.5) | 6 (40.0) |
| Surgery + RT | 7 (26.9) | 1 (9.1) | 6 (40.0) |
| Surgery + CT + RT | 4 (15.4) | 2 (18.2) | 2 (13.3) |
| Chemotherapy protocol | | | |
| Cisplatin | 13 (81.3) | 6 (75.0) | 7 (87.5) |
| Cetuximab | 3 (18.8) | 2 (25.0) | 1 (12.5) |
| Radiotherapy protocol | | | |
| 70 Gy: 2 Gy/day | 26 (100.0) | 11 (100.0) | 15 (100.0) |
| Surgery protocol | | | |
| Total resection | 1 (9.1) | 0 (0.0) | 1 (12.5) |
| Partial resection[d] | 10 (90.9) | 3 (100.0) | 7 (87.5) |
| Survival | | | |
| Follow-up (months), mean ± SD | 45.7 ± 17.9 | | |
| OS rate (%), mean ± SD | 40.2 ± 2.87 | | |
| DFS rate (%), mean ± SD | 27.2 ± 2.68 | | |
| Local-regional recurrence | 11 (42.3) | | |
| Distant relapse | 5 (19.2) | | |
| Metastasis | 5 (19.2) | | |

CT, chemotherapy; DFS, disease-free survival; OS, overall survival; RT, radiotherapy; SD, standard deviation.

[a] Statistical significance: $*P < 0.05$.

[b] Following the Union for International Cancer Control (UICC) TNM Classification of Malignant Tumours, 7th edition. Data on cancer stage were missing for two patients in the control group.

[c] Data were missing for one patient in the laser group and two patients in the control group, due to doubtful or unreliable classification.

[d] Partial resection: Patients with edges of the excision affected by the lesion, or who had nodes with rupture of the ganglionic capsule due to neoplastic lesions.

ty make mucositis one of the primary complications of oncological treatment linked to debilitating side effects. In both the short and long term, this can seriously impair the patient's quality of life, leading to complications such as chronic aspiration, starvation, secondary infections that may progress to bacteremia, and severe pain; these conditions often require that the patient be hospitalized[18]. On some occasions, severe mucositis (grades 3–4) may necessitate the interruption or modification of oncological treatment, potentially resulting in treatment failure[8,18,19]. Different treatment options have been tested for the prevention and treatment of mucositis, but a gold standard treatment has yet to be conclusively identified[20].

A recent systematic review and meta-analysis analysed the effect of LLLT on chemotherapy-induced oral mucositis in paediatric and young patients[21]. It was concluded that prophylactic LLLT reduces mucositis and decreases the average severity of oral mucositis and oral pain in paediatric and young patients with cancer. Other articles have corroborated these results in paediatric patients undergoing haematopoietic stem cell transplantation[22,23].

Although all patients in this study were adults, recent systematic reviews and meta-analyses have shown that out of all of the measures adopted for the treatment of oral mucositis or pain resulting from oncological treatment, benzydamine mouthwash, LLLT with or without basic standard oral care, and 2% morphine mouthwash showed a statistically significant benefit[4–6,9]. These analyses are in concordance with the results obtained in the present study, in which statistically significant differences were observed between the LLLT group and control group ($P < 0.05$). Thus, LLLT is a relevant factor for the prevention of oral mucositis in paediatric and adult patients undergoing oncological treatment. In addition, LLLT helps to reduce others adverse effects occurring as a consequence of oncological treatment, such as interruption of oncological therapy ($P = 0.030$), the need for parenteral nutrition during head and neck radiotherapy ($P = 0.027$), and trismus ($P = 0.023$)[24]. The lower incidence of oral mucositis associated with photobiomodulation therapy might be correlated to the activation of genes involved in keratinocyte differentiation[25].

Recently new questions have arisen regarding photobiomodulation: Could LLLT impact tumour growth or proliferation? Could LLLT affect the risk of local invasion or metastases? Could LLLT negatively affect the tumour response to treatment (particularly radio-resistance in the case of radiotherapy in oral SCC)? Also, is it possible that the local application of LLLT could have effects distant from the targeted site[7]? Brandão et al.[26] performed a retrospective clinical analysis of 152 patients with advanced oral SCC treated with prophylactic LLLT for radiotherapy-induced oral mucositis and found that when used prophylactically, LLLT showed no effect on the treatment outcomes of the primary cancer, the recurrence or appearance of new primary tumours, or the survival rates of patients with advanced oral SCC.

Antunes et al.[27] evaluated 94 patients diagnosed with cancer of the oropharynx, nasopharynx, or hypopharynx, subjected to conventional radiotherapy plus cisplatin every 3 weeks. LLLT was applied with an InGaAlP (indium–gallium–aluminium phosphide) diode laser (660 nm,

*Table 3*. Various parameters related to monitoring.

| Variables | Total | | Group | | | | *p*-Value |
|---|---|---|---|---|---|---|---|
| | | | Laser | | Control | | |
| | Mean | Mean | Mean | SD | Mean | SD | |
| Weeks of oncological treatment | 10.62 | 1.60 | 10.82 | 1.54 | 10.47 | 1.68 | |
| Maximum time with clinical mucositis (weeks) | 5.77 | 3.43 | 3.64 | 3.11 | 7.33 | 2.82 | <0.01 |
| % Maximum time with clinical mucositis/weeks of treatment | 55.54 | 32.06 | 35.64 | 31.23 | 70.14 | 24.47 | <0.01 |
| Weeks with mucositis grade > 0 | 6.08 | 3.26 | 4.00 | 2.90 | 7.60 | 2.67 | <0.01 |
| Number of weeks with areas grade > 0 | 6.19 | 3.24 | 4.27 | 3.00 | 7.60 | 2.69 | <0.01 |
| % Weeks with mucositis grade > 0 | 58.28 | 30.45 | 38.46 | 28.80 | 72.81 | 22.99 | <0.01 |
| % Weeks with areas grade > 0 | 59.26 | 29.94 | 40.94 | 29.48 | 72.70 | 22.87 | <0.01 |
| Mean number of affected areas | 1.47 | 1.22 | 0.60 | 0.53 | 2.11 | 1.19 | <0.001 |

SD, standard deviation.

100 mW, 1 J, 4 J/cm$^2$) and it was found that the group receiving LLLT had a better response to treatment (chemoradiotherapy), which translated to a longer progression-free survival than those in the placebo group ($P = 0.030$). They also found no statically significant difference between the placebo group and laser group regarding overall survival ($P = 0.90$) or disease-free survival ($P = 0.659$).

In conclusion, photobiomodulation with LLLT reduces the incidence and severity of mucositis in patients treated with radiotherapy and/or chemotherapy. Further studies are needed to determine the biological mechanism through which the laser improves wound healing and reduces pain.

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## Competing interests

None to declare.

## Ethical approval

The study was approved by the Ethics Committee of Virgen del Rocío University Hospital (register number FPS-LAS-2012-04/Acta 4/13; date of approval, 04/24/2013).

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijom.2018.12.006.

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