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Cost-effectiveness of low-level laser therapy (LLLT) in head and neck cancer patients receiving concurrent chemoradiation ☆

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SUMMARY

Background: Oral mucositis is a major event increasing treatment costs of head and neck squamous cell carcinoma (HNSCC) patients treated with chemoradiation (CRT). This study was designed to estimate the cost-effectiveness of low-level laser therapy (LLLT) to prevent oral mucositis in HNSCC patients receiving CRT.

Methods: From June 2007 to December 2010, 94 patients with HNSCC of nasopharynx, oropharynx, and hypopharynx entered a prospective, randomized, double blind, placebo-controlled, phase III trial. CRT consisted of conventional radiotherapy (RT: 70.2 Gy, 1.8 Gy/d, 5 times/wk) + concurrent cisplatin (100 mg/m^2) every 3 weeks. An InGaAlP (660 nm–100 mW–4 J/cm^2) laser diode was used for LLLT.

Results: From the perspective of Brazil's public health care system (SUS), total costs were higher in Placebo Group (PG) than Laser Group (LG) for opioid use (LG = US$ 9.08, PG = US$ 44.28), gastrostomy feeding (LG = US$ 50.50, PG = US$ 129.86), and hospitalization (PG = US$ 77.03). In LG, the cost was higher for laser therapy only (US$ 1880.57). The total incremental cost associated with the use of LLLT was US$ 1689.00 per patient. The incremental cost-effectiveness ratio (ICER) was US$ 4961.37 per grade 3–4 OM case prevented compared to no treatment.

Conclusions: Our results indicate that morbidity was lower in the Laser Group and that LLLT was more cost-effective than placebo up to a threshold of at least US$ 5000 per mucositis case prevented. Clinical trial information: NCT01439724.

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Introduction

Oral mucositis (OM) is the most debilitating complication in patients with malignancies of the head and neck receiving radiotherapy and chemotherapy and has the most significant impact on treatment and cost of care. OM affects approximately 80–100% of chemotherapy- and radiotherapy-treated patients [1–6] at varying levels and is triggered by radiation doses between 15 and 20 Gy [6–8]. Additionally, OM has a direct impact on patients because it may result in increased pain, feeding difficulties, need for gastrostomy feeding, decreased performance status and subsequent worsening of quality of life (QoL), and increased treatment costs [9] Moreover, the small number of studies on the

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economic impact of OM belies its importance and complexity. In fact, only two retrospective studies have reported on the impact of OM on treatment costs: in the first study, OM was associated with an incremental cost of US$ 1700–6000 depending on grade [9], whereas in the second, the incremental inpatient hospitalization costs were US$ 14,000 [10]. Several clinical trials have shown that low-level laser therapy (LLLT) is effective for the prevention of OM in patients with head and neck cancer (HNC) receiving chemo- and radiotherapy, but there are no studies on either the costs associated with the use of prophylactic laser therapy [11–18] or its cost-effectiveness for prevention of mucositis.

Evidence for the efficacy of laser therapy in preventing OM in the context of a controlled and randomized trial has been provided by our group [18]. Nevertheless, economic evidence should also be provided so that policy makers can use it for the possible incorporation of LLLT into the list of procedures covered by any given health care system. This study aimed to estimate the cost-effectiveness of LLLT to prevent oral mucositis in head and neck squamous cell carcinoma (HNSCC) patients, from the perspective of Brazil's public health care system.

Methods

We used primary data from 94 patients diagnosed with cancer of the nasopharynx, oropharynx, and hypopharynx who participated in a prospective, randomized, double blind, placebo-controlled, phase III trial at the National Cancer Institute (INCA), Rio de Janeiro, Brazil, from June 2007 to December 2010. Patients were randomly assigned into two groups of 47 patients each: the Laser Group (hereafter LG) and the Placebo Group (hereafter PG). The performance status [19] and inclusion/exclusion criteria adopted in our study are the same as described elsewhere [18].

The analysis was conducted from the perspective of Brazil's public health care system. Discount rates for costs and health effects were not applied because the time horizon of the analysis was one year.

Study design

A decision tree model was developed to describe the sequence of events observed in the Laser and Placebo groups (Fig. 1). We compared the use of prophylactic laser therapy for the prevention of oral mucositis in HNSCC patients undergoing treatment with chemotherapy (CT) and radiotherapy (RT) to a placebo group, which received the same treatment with the use of a laser that emitted no beam. For calculation purposes, the application of placebo was not considered and this group was considered the no-intervention group (NIG).

Analysis of costs

Costs of laser therapy

Low-level laser therapy is not covered by the public health care system, and thus there are no cost estimates for the procedure from the public payer's perspective. We used a micro-costing approach based on the procedure performed at a public health unit, the National Cancer Institute (INCA). The steps, inputs, and human resources involved in the process were determined through interviews with health professionals, observation of activities, and quantification of materials and man-hours required by each professional.

The average total cost per laser session was calculated as the annual sum of total variable costs, fixed costs, and semi-fixed costs divided by the annual number of laser sessions performed at INCA.

Fixed costs included administrative costs and durable goods such as furniture to set up the dentist office, waiting room, reception, and common areas such as restrooms and kitchen, and equipment. Durable goods prices were depreciated considering a lifespan of 10 years for furniture and five years for computer equipment, ordinary office equipment, and laser equipment. The equivalent annual cost (EAC) of durable goods was estimated as a function of their lifespan, purchase value, and discount rate (5%) according to the formula:

$$\mathrm{EAC} = t * X/1 - 1/(1+t)^n,$$

where EAC = equivalent annual cost; t = lifespan; X = purchase price of item; n = discount rate.

Administrative inputs (overhead costs) included water, electricity, security, telephone services, cleaning, and waste disposal. Overhead costs were estimated by prorating the monthly values per m^2 of area occupied by the dentist service.

Variable inputs included 70% ethanol, gauze, and procedure gloves. Labor costs were considered semi-fixed costs, because they incorporated a fixed rate up to a certain number of procedures per day that staff were able to perform; beyond that number, costs were varied with the addition of additional staff. A four-person staff composed of two dentists, one technical-administrative assistant, and one receptionist was the smallest staff size required for

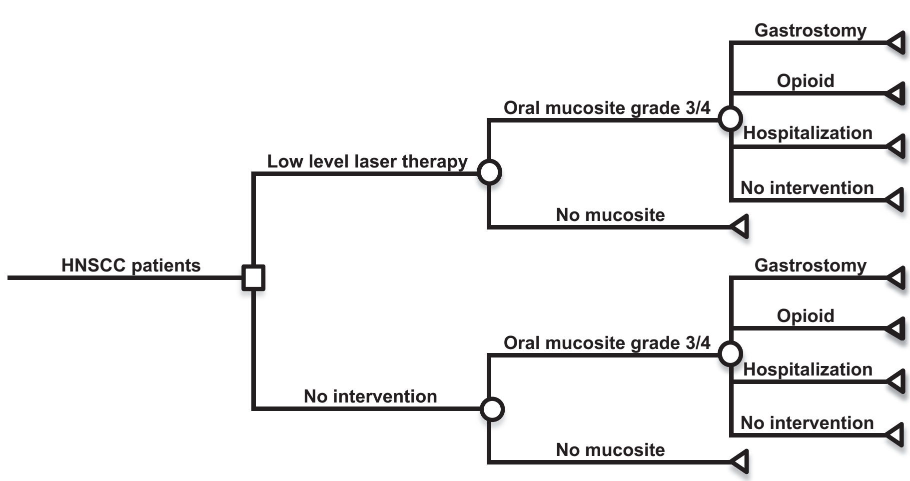

Fig. 1. Decision tree analitic model comparing low level laser therapy (intervention arm) and no intervention (control arm). Square denotes decision node; circles are chance nodes; and triangles are terminal nodes.

the operation of the laser service five days a week, eight working hours per day, 240 working days per year.

The cost and resource consumption data were obtained from the architecture, planning, and management sectors at INCA. Unit costs of inputs were determined using the Unified Health System Table of Procedures, Medications, Orthoses, Prostheses, and Materials Management System (SIGTAP/SUS), and the price of laser equipment (Photon Laser III, DMC, São Carlos, São Paulo, Brazil) was retrieved from the procurement system of the Brazilian federal government (http://www.comprasgovernamentais.gov.br/).

Cost estimates were originally calculated in the local currency (reais, R$) and then converted to 2013 US dollars (US$) at a purchasing power parity conversion factor of 1.61 reais per dollar.

Univariate sensitivity analysis was used to evaluate the uncertainty in the parameters associated with LLLT and determine the cost drivers of laser therapy. The following parameters were varied: number of laser sessions (a minimum of eight and a maximum of 24 sessions per day, the highest possible number of sessions at the laser service), price of laser equipment (±20%), discount rate (0–10%), fixed costs (±20%), variable costs (±20%), and wages (±20%).

Costs of oral mucositis

The costs associated with OM included episodes of grade 3–4 mucositis and the need for use of opioids, gastrostomy and nasogastric tube placement, and hospitalization.

The resources used by patients in the LG and PG were listed during the clinical trial [18] and used to quantify the treatment costs of OM [20]. Hospitalization rates directly associated with the treatment of OM were not observed in this study, and thus we assumed the rate (30%) from Murphy et al. [5] Costs associated with RT and CT, fluconazole, 0.12% chlorhexidine, and dropout rates for RT and CT were excluded because they were equivalent in both groups [18].

The costs of medications were obtained from the Databank of Prices in the Health System (BPS System), using the average purchase price of medicines acquired by the public health [21]. Costs for procedures and hospitalizations were obtained from the Unified Health System Table of Procedures, Medications, Orthoses, Prostheses, and Materials Management System (SIGTAP/SUS), January 2012 [22].

Cost-effectiveness analysis

The incremental cost-effectiveness ratio (ICER) was calculated to determine the relative cost-effectiveness of the prophylactic use of laser therapy. The ICER is the ratio between the difference in costs ($Cost_B - Cost_A$) and the difference in effects/benefits ($Effect_B - Effect_A$) of a therapeutic intervention or treatment, in which A and B represent different strategies (treatment groups), in our study, PG and LG, respectively. In our analysis, the ICER represents the incremental cost per additional grade 3–4 oral mucositis event prevented.

Univariate sensitivity analysis was used to assess the uncertainty in the parameters of the economic model. The base-case values and intervals considered are shown in Table 1. The cost of laser therapy was varied based on the highest estimated value for the minimum number of laser sessions per working day (8 sessions) up to the maximum operational capacity (24 sessions per day). The cost of medications was varied by ±20% to simulate their floating prices on the market. The SUS reimbursement values for gastrostomy and hospitalization were varied by ±20% to simulate possible adjustments to the price list. Treatment duration for OM using medications was varied based on the minimum and maximum treatment duration observed in the clinical trial study [18]. Hospitalization rates were obtained from the study by Murphy et al. [5] Cases of oral mucositis were varied between 40% [18] and 66% [9] based on the expected frequency of cases.

Table 1
Base-case values and intervals considered.

Parameters	Base case	Range	Reference
Laser therapy cost	US$ 41.18	US$ 23.44–71.45	micro-costing
Opioid drugs cost	US$ 6.53	±20%	BPS database
Gastrostomy cost	US$ 339.08	+20%	BPS database
Hospitalization cost	US$ 256.75	+20%	BPS database
Duration of opioid therapy	50 days	0–100 days	Antunes et al.
Hospitalization frequency	30%	0–50%	Murphy et al.
Grade 3–4 oral mucosite frequency	40%	40–66%	Antunes et al.

Laser therapy protocol

An InGaAlP (Indium–Gallium–Aluminum Phosphide) diode laser (DMC, São Carlos, São Paulo, Brazil) with a continuous wavelength of 660 nm, 100 mW, 1 J, 4 J/cm^2, and a spot size of 0.24 cm^2 was used for laser therapy.

Preventive laser application was performed daily from Monday to Friday by two dentists and before application of radiotherapy. The laser was applied in contact with the mucosa on nine points per region for 10 s per point, totaling 12 min per patient. Low-level laser therapy consisted of one session per day for patients in the Laser Group and averaged 45.7 days. Additional treatment details are described elsewhere, in a study previously done by our group [18].

Clinical parameters

We recorded all complications observed during treatment (need for gastrostomy or nasogastric tubes, weight loss, opioid use, treatment interruption or delay, and hospitalization). Adverse events were evaluated daily according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) for Oral Mucositis, version 3.0 [23], whereas the oral cavity of patients was evaluated daily according to the World Health Organization (WHO) Oral Toxicity Score [24] and the Oral Mucositis Assessment Scale (OMAS) [25].

Body mass index (BMI) was assessed on the first day of treatment and weekly thereafter. In case of pain in the oral cavity or oropharynx, opioid and non-opioid analgesics were used according to the WHO criteria [26].

Percutaneous gastrostomy or nasogastric tubes were indicated for nutritional support of patients with grade 4 OM, pain score (visual analogue scale, VAS) $\geqslant$6 after use of opioid analgesics, or patients who lost $\geqslant$10% body weight.

Statistical analysis

The cost-effectiveness analysis was performed using data from the study by Antunes et al. [18], whose primary endpoint was the incidence of grade 3–4 mucositis based on the WHO score. One-sided tests assumed an $\alpha = 0.05$ and a $\beta = 0.20$ for a sample of 94 patients and an estimated OM incidence of 15% for the Laser Group [27] and 40% for the Placebo Group 40% [1]. *P*-values were derived from two-sided tests. The significance level was set at $P \leqslant 0.05$. The analyses were performed using SPSS Statistical Software 18.0.

A descriptive analysis based on OM frequency and use of opioids and gastrostomy was used to determine the cost-effectiveness of low-level laser therapy.

The chi-square test (χ^2) was used to compare patient characteristics, incidence of OM, need for gastrostomy or nasogastric tubes, pain scores (VAS), treatment interruption, hospitalization, and patient exclusion between the Laser and Placebo groups.

Results

Cost of laser therapy

The dentist service recorded 3264 laser sessions in 2012, approximately 14 applications per working day. The average time for each prophylactic laser session was 20 min per patient.

The estimated average cost per session was US$ 41.18, considering 14 applications for 240 working days per year (Table 2).

The sensitivity analysis showed that the number of daily procedures, salary of staff, and administrative costs, in that order, had the greatest impact on the cost of laser therapy. However, if the service operated at full capacity, i.e., 24 sessions per day, the cost of laser therapy would be reduced by 40%.

The incidence of grade 3–4 OM in the study by Antunes et al. [18] was 6.4% in the LG and 40.5% in the PG, which equated to a relative risk reduction (RRR) of 0.158 (95% CI: 0.050–0.498). The patient characteristics and the frequency of gastrostomy, hospitalization, and opioid use are summarized in Table 3.

Based on the toxicity of cancer therapy and the perspective of Brazil's public health care system (SUS), total costs were higher in the Placebo Group than in the Laser Group for opioid use (LG = US$ 9.07; PG = US$ 44.26), gastrostomy (LG = US$ 50.50; PG = US$ 129.86), and hospitalization (PG = US$ 77.03). In the Laser Group, the cost was higher for laser therapy only (US$ 1880.57).

The incremental cost associated with the use of laser was US$ 1689.00 per patient. The incremental cost-effectiveness ratio (ICER) was US$ 4961.37 per grade 3–4 OM case prevented compared to the untreated group (Table 4).

The deterministic sensitivity analysis showed that the incremental cost-effectiveness ratio (ICER) would increase by 82% if the cost of laser therapy were US$ 71.45, which was the highest cost for laser therapy in a scenario with eight sessions per day. Conversely, in a scenario in which the frequency of OM was 60% in the no-intervention group [18], ICER would be reduced by 43%. The tornado diagram (Fig. 2) represents the percent changes in ICER as a function of the variation in the parameters considered in the analysis.

Table 2
Total cost and annual cost of parameters for patients of laser therapy.

Parameters	Total cost	Annual cost
Fixed costs		
Furniture (table, chair, computer, reception counter, cabinet, toilet supplies)	$9165.91	$1781.50
Dental office	$8258.94	$1782.72
Laser equipment	$2892.80	$668.16
Overhead (electricity, water, cleaning, waste disposal, security, telephony)		$11041.55
Semi-fixed costs		
Professional wages (2 dentist, 1 auxiliar, 1 receptionist)		$120,578.56
Variable costs		
Medical supplies (alcohol 70°, gauze, glove)		$2823.17
Mean cost of prophylactic laser therapy		$41.18

Table 3
Baseline characteristics of the patients.

Characteristics	Laser group (n = 47)	Placebo group (n = 47)	P value
Age – yr (SD)			
Average	53.5 (±6.9)	55.7 (±8.6)	0.163[*]
Sex – no (%)			0.536[***]
Masculine	42 (89.4)	40 (85.1)	
Feminine	5 (10.6)	7 (14.9)	
Primary site – no (%)			0.107[**]
Nasopharynx	7 (14.9)	2 (4.3)	
Oropharynx	33 (70.2)	41 (87.2)	
Hypopharynx	7 (14.9)	4 (8.5)	
Staging – no (%)			0.696[**]
Stage I[a]	1 (2.1)	0	
Stage II	8 (17.0)	6 (12.8)	
Stage III	14 (29.8)	16 (34.0)	
Stage IV	24 (51.1)	25 (53.2)	
Radiotherapy – no (%)			0.778[**]
Cobalt^{60}	39 (82.9)	40 (85.1)	
Linear accelerator photons	8 (17.1)	7 (14.9)	
Oral mucositis			<0.001[**]
Grade 0–1	28	10	
Grade 2	16	18	
Grade 3	2	17	
Grade 4	1	2	
Opioid use	15 (31.9%)	40 (85.1%)	<0.001[**]
Gastrostomy	7 (14.9%)	18 (38.3%)	0.010[**]
Hospitalization	0 (0%)	0 (0%)	NA

[*] P values were calculated by Student test.
[**] P values were calculated by chi-square test.
[***] P values were calculated by Fisher's exact test.
[a] This patient refused surgery and was treated exclusively by CRT.

Table 4
Total cost for patients.

Parameters		
Mean cost per patient (US$)	Laser therapy	No intervention
Low level laser therapy	1880.57	0.00
Hospitalization	0.00	77.03
Opioids use	9.08	44.28
Gastrostomy	50.50	129.86
Outcome (n)		
Oral mucosite grade 3–4	3	23
Incremental cost	1688.98	
Incremental effect (cases avoided)	34%	
Incremental cost-effectiveness ratio (ICER)	4961.37	

Discussion

Severe oral mucositis has a high impact on the costs associated with the treatment of head and neck cancer in patients receiving radiotherapy and chemotherapy due to the resources used for treating pain and fungal/bacterial infections and, at times, need for gastrostomy feeding tubes and hospitalization. Nevertheless, the incidence of OM can be reduced through the preventive use of low-level laser in the oral cavity of HNC patients for the duration of treatment. However, even though the addition of a procedure to the patient's routine reduces the incidence of OM, it also adds additional costs to treatment.

To our knowledge, this is the first study to determine the cost of laser therapy. Laser therapy has been used in Brazil's public health system for clinical trial purposes only and resources consumed have been funded with research funds. This study used a micro-costing approach to estimate the cost of laser therapy at a cancer center with a dentist service that routinely performs laser therapy.

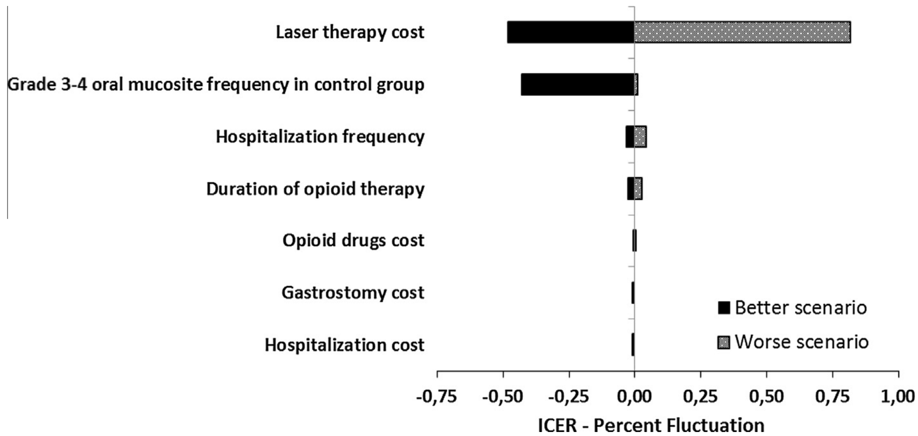

Fig. 2. Percent fluctuation of ICER.

The lack of information about the cost of laser therapy has hampered discussions about the inclusion of this procedure in the list of procedures reimbursed by the Unified Health System (SUS) and also has precluded the execution of economic analyses. The estimated average cost per prophylactic laser session was US$ 41.18, considering the dentist service characteristics evaluated at an operational capacity of 14 sessions per working day. However, the daily operational capacity, salary of staff, and administrative costs had the greatest impact on the cost of laser therapy. Thus, because these factors are often specific to each dental unit, they should be considered when discussing the widespread addition of laser therapy in other dentist services.

When laser therapy costs are excluded, the per-patient cost was US$ 251.14 higher in the Placebo Group than in the Laser Group due to the toxicity of oral mucositis. Similar findings have been reported by Elting et al. [9], Nonzee et al. [10], and Murphy et al. [5], although costs were greater in those studies due to differences in the health and reimbursement systems.

The benefits of a new treatment to the quality of life (QoL) of patients should always be considered when comparing health gains and costs among interventions. QoL is known to decrease with the increasing toxicity of treatment [18,28] and the only way to reduce the suffering of patients and the costs of OM is investing in the prevention of OM.

Several studies have shown satisfactory results in the prevention of OM in HNC patients, but the use of low-level laser therapy by Antunes et al. [18] has changed the paradigm of OM prevention. In that study, the only one to have evaluated QoL in patients receiving chemoradiotherapy and preventive laser therapy, Antunes et al. [18] administered the EORTC-QLQ-C30 overall quality of life questionnaire and the EORTC-QLQ-H&N-35 head and neck cancer quality of life questionnaire on the first day of RT (1st fraction), during RT (20th fraction), and at the end of RT (39th fraction). The authors found that QoL was negatively affected in patients who did not receive preventive laser therapy. In fact, on the last day of RT (39th fraction), EORTC-QLQ-C30 and EORTC-QLQ-H&N35 results indicated that patients in the control group (placebo) had a significantly poorer outcome than patients receiving LLLT.

The main limitation of this study is that we evaluated the intermediate outcome of grade 3–4 oral mucositis cases prevented. In fact, working with final outcomes such as life years gained or quality-adjusted life-years in cost-effectiveness analysis enables the comparison of studies that examine different technologies. In a scenario where limited resources should be better allocated, and with a number of technologies yet to be covered by the public health care system, decisions should be made to maximize health gains at minimal costs, but the health gains can only be compared when the same outcome is considered. Survival data are usually the main predictor of efficacy but no data are available for the use of prophylactic laser therapy for the prevention of oral mucositis. Even though Antunes et al. [18] analyzed survival data for patients receiving preventive laser therapy, the authors found no significant difference between the treatment and control groups. Nevertheless, LLLT had a positive impact on the QoL of HNC patients receiving RT and CT. Therefore, in our study, the health gains were expressed in terms of the number of cases prevented in the cost-effectiveness analysis. Thus, in this scenario, the improved QoL of HNC patients is associated with additional treatment costs.

Despite the significant reduction in the incidence of OM and the reduced costs with gastrostomy, opioids, and hospitalizations, the cost of laser therapy had the greatest impact on treatment cost. A more efficient use of resources may make the technique more cost-effective from the health system's perspective. This greater efficiency could be achieved by increasing the number of laser sessions per day up to maximum operational capacity according to existing facilities and staff. Additionally, the incorporation of the procedure into the list of reimbursable procedures of the Brazilian health system would extend the service offering to the population, and the spread of technology could reduce the costs of laser equipment in Brazil.

Our results showed that morbidity was lower in the Laser Group and that LLLT was more cost-effective than placebo up to a threshold of at least US$ 5000 per oral mucositis case prevented.

Our report is also of interest to other countries offering public health care as well as private institutions interested in reducing costs of health care.

Clinical trial information: NCT01439724.

Conflict of interest

The authors declare they have no conflict of interest and that the study was not funded by DMC (São Carlos, São Paulo, Brazil).

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