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Low level laser therapy/photobiomodulation in the management of side effects of chemoradiation therapy in head and neck cancer: part 1: mechanisms of action, dosimetric, and safety considerations

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Disclaimer

This article is based on a narrative review of existing data and the clinical observations of an international multidisciplinary panel of clinicians and researchers with expertise in the area of supportive care in cancer and/or PBM clinical application and dosimetry. This article is informational in nature. As with all clinical materials, this paper should be used with the clear understanding that continued research and practice could result in new insights and recommendations. The review reflects the collective opinion and as such does not necessarily represent the opinion of any individual author. In no event shall the authors be liable for any decision made or action taken in reliance on the proposed protocols.

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Abstract

Purpose—There is a large body of evidence supporting the efficacy of low level laser therapy (LLLT), more recently termed photobiomodulation (PBM), for the management of oral mucositis (OM) in patients undergoing radiotherapy for head and neck cancer (HNC). Recent advances in PBM technology, together with a better understanding of mechanisms involved, may expand the applications for PBM in the management of other complications associated with HNC treatment. This article (part 1) describes PBM mechanisms of action, dosimetry, and safety aspects and, in doing so, provides a basis for a companion paper (part 2) which describes the potential breadth of potential applications of PBM in the management of side-effects of (chemo)radiation therapy in patients being treated for HNC and proposes PBM parameters.

Methods—This study is a narrative non-systematic review.

Results—We review PBM mechanisms of action and dosimetric considerations. Virtually, all conditions modulated by PBM (e.g., ulceration, inflammation, lymphedema, pain, fibrosis, neurological and muscular injury) are thought to be involved in the pathogenesis of (chemo)radiation therapy-induced complications in patients treated for HNC. The impact of PBM on tumor behavior and tumor response to treatment has been insufficiently studied. In vitro studies assessing the effect of PBM on tumor cells report conflicting results, perhaps attributable to inconsistencies of PBM power and dose. Nonetheless, the biological bases for the broad clinical activities ascribed to PBM have also been noted to be similar to those activities and pathways associated with negative tumor behaviors and impeded response to treatment. While there are no anecdotal descriptions of poor tumor outcomes in patients treated with PBM, confirming its neutrality with respect to cancer responsiveness is a critical priority.

Conclusion—Based on its therapeutic effects, PBM may have utility in a broad range of oral, oropharyngeal, facial, and neck complications of HNC treatment. Although evidence suggests that PBM using LLLT is safe in HNC patients, more research is imperative and vigilance remains warranted to detect any potential adverse effects of PBM on cancer treatment outcomes and survival.

Keywords

Low level laser therapy; Low level light therapy; Photobiomodulation; Mucositis; Orofacial complications; Chemotherapy; Radiation therapy; Head and neck cancer; Safety; LLLT and PBM

Introduction

Nearly all patients with advanced head and neck cancer (HNC) suffer complications from treatment with radiation therapy (RT) or chemoradiotherapy (CRT) [1]. CRT is currently the standard of care with or without surgery in advanced HNC. An increased frequency and severity of side effects is seen, particularly when chemotherapy (CT) is combined with accelerated or hyperfractionated RT regimens. It is now recognized that organ preservation in HNC treatment is not synonymous with function preservation, and effects on quality of life (QoL) must be considered in cancer treatment planning and extending survival [2, 3].

RT to the head and neck, with or without CT, damages adjacent tissues within the radiation field despite continuing efforts to minimize these effects [1]. Furthermore, targeted therapies administered as single agents, and combined with RT or CRT, may generate additional symptoms [4–6]. Acute complications include oral mucositis (OM), pain, dysphagia, infections, salivary changes, dysgeusia, and dermatitis. Common chronic complications include hyposalivation and xerostomia, mucosal infections, mucosal atrophy, neuropathies including mucosal pain, dysgeusia, tooth demineralization and rampant caries, progression of periodontitis, soft tissue and/or bone necrosis, mucocutaneous and muscular fibrosis, dysphagia, trismus, lymphedema, dermatitis, and voice and speech alterations [7]. These complications are associated with morbidity and mortality, increased use of health care resources and costs, and may compromise patient adherence to cancer therapy protocols resulting in suboptimal outcomes.

Among the few supportive care measures available, low level laser or light therapy (LLLT) has shown significant promise. LLLT refers to light therapy that may stimulate tissue regeneration, reduce inflammation, and control pain. These treatments were originally referred to as “low level laser” because the light is of low intensity compared with other forms of medical laser treatment, which are used for ablation, cutting, and coagulation. At the 2014 joint North American Association for Laser Therapy (NAALT) and World Association for Laser Therapy (WALT) conference, photobiomodulation (PBM) was accepted as the preferred name with the following definition: “The therapeutic use of light [e.g. visible, near infrared (NIR), infrared (IR)] absorbed by endogenous chromophores, triggering non-thermal, non-cytotoxic, biological reactions through photochemical or photophysical events, leading to physiological changes” [8].

The potential utility of PBM in the management of side-effects of chemoradiation therapy in head and neck cancer

Although the biological mechanisms underlying the therapeutic effects of PBM have not been fully elucidated, studies suggest that PBM enhances wound healing [9], significantly

reduces inflammation, and prevents fibrosis [10–15]. Moreover, PBM reduces pain and improves function [16–19]. These photobiological reactions have been shown to occur in various tissues.

Systematic reviews have suggested efficacy of PBM for OM management in hematopoietic stem cell transplant (HSCT) recipients and in HNC patients [20–25]. Whereas in most studies, PBM is applied intra-orally on the oral mucosal tissues, studies indicate that it may also be administered extra-orally, with a resultant effect on structures at risk for OM transcutaneously, thereby enhancing the ease of delivery and possibly the efficacy of treatment [23, 26].

In addition, new generation PBM devices consisting of a cluster of laser or light-emitting diode (LED) beams, instead of a single laser point, provide exposure of larger fields. Monochromatic high-quality LED beams have the same properties as diode lasers with the same wavelength, but their light beam is less coherent. LED specifics need to be carefully matched to PBM using lasers when considering LED arrays.

When used with appropriate parameters, the light is able to penetrate into tissues sufficiently to activate cellular processes [27]. This finding suggests that extra-oral administration of PBM (with or without concurrent use of intra-orally administered PBM) enables the light to reach other anatomical structures of the head and neck at risk for RT- and CRT-induced complications. This may broaden the range of indications for PBM for the prevention and treatment of cancer treatment-induced complications.

Goals of this work

A task force consisting of an international multidisciplinary panel of clinicians and researchers with expertise in the area of supportive care in cancer and/or PBM clinical application and dosimetry was formed. The mission of this group is to aid in the design of PBM study protocols, identify validated outcome measures, and test the efficacy and safety of PBM for the management of complications related to cancer therapy.

In this paper, we review and discuss PBM mechanisms of action, dosimetry, and safety considerations. In a subsequent paper (part 2), we (i) identify selected oral, oropharyngeal, facial, and neck complications of treatment for HNC, in which PBM may have potential for prophylaxis and/or treatment; (ii) propose PBM parameters for prophylaxis and therapy to mitigate these complications based on current evidence and knowledge; and (iii) discuss directions of future research related to the use of PBM in HNC.

PBM mechanisms of action and therapeutic effects

The conclusion that PBM effectively modulates biological function is supported by a plethora of clinical and laboratory studies [17, 28]. Despite variations in instrumentation and dosing parameters, since its introduction in 1967, PBM has been shown to enhance wound repair and tissue regeneration by influencing different phases of injury resolution including the following: (i) the inflammatory phase, in which immune cells migrate to the site of tissue injury, ii) the proliferative phase, which includes stimulation of fibroblasts and macrophages

as well as other repair components, and iii) the remodeling phase, consisting of collagen deposition and rebuilding of the extracellular matrix at the wound site [29].

Although the complex biological mechanisms underlying the therapeutic effects of PBM have not been completely elucidated and may vary among different cell types and tissue states (healthy versus stressed or hypoxic), laboratory and clinical studies suggest that PBM significantly reduces inflammation and prevents fibrosis [10–15]. It has become increasingly clear that PBM's biological effects are closely dose-related. In fact, the historical lack of dosing consistency has been a confounder in the comprehensive interpretation of PBM activity. Nonetheless, confirmatory studies have contributed to a fundamental understanding of PBM biology.

Current data suggest that PBM acts predominantly on cytochrome c oxidase (CcO) in the mitochondrial respiratory chain by facilitating electron transport resulting in an increased transmembrane proton gradient that drives adenosine triphosphate (ATP) production [30]. ATP is the universal energy source in living cells essential for all biologic reactions, and even a small increase in ATP levels can enhance bioavailability to power the functions of cellular metabolism [31]. In addition, the absorption of red or NIR light may cause a short, transient burst of reactive oxygen species (ROS) that is followed by an adaptive reduction in oxidative stress. This action, impairment of ROS production, has been shown to favorably mitigate radiation-induced injury and mimics the activity of molecular agents that attenuate tissue damage (examples include amifostine, N-acetyl cysteine, and superoxide dismutase).

Low concentrations of ROS impact many cellular processes, including activation of key transcription factors such as nuclear factor kappa B (NF-κB). This results in the expression of stimulatory and protective genes [32], which generate growth factors belonging to the fibroblast growth factor family, pro-inflammatory cytokines, and chemokines that are involved in tissue repair.

In hypoxic or otherwise stressed cells, mitochondria produce nitric oxide (mtNO), which binds to CcO and displaces oxygen [33]. This binding results in inhibition of cellular respiration, decreased ATP production, and increased oxidative stress (a state that develops when the levels of ROS exceed the defense mechanisms), leading to the activation of intracellular signaling pathways, including several transcription factors [34]. These include redox factor-1 (Ref-1), activator protein-1 (AP-1), NF-κB, p53, activating transcription factor/cAMP-response element–binding protein (ATF/CREB), hypoxia-inducible factor (HIF)-1, and HIF-like factor [35]. These transcription factors induce downstream production of both inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1 and IL-6, cyclooxygenase (COX)-2, and prostaglandin E2 (PGE-2) [34, 36, 37] and anti-inflammatory mediators [transforming growth factor (TGF)-beta, IL-10]. There is evidence suggesting that when PBM is administered with appropriate parameters to stressed cells, NO is dissociated from its competitive binding to CcO, ATP production is increased, and the balance between prooxidant and antioxidant mediators is restored, resulting in a reduction of oxidative stress [38]. For example, PBM has been shown to attenuate the production of ROS by human neutrophils [39]. Silveira et al. [40] reported that PBM reduced ROS in an animal model of traumatic tissue injury, whereas a study in a model of

acute lung inflammation found PBM to reduce the generation of TNF-α and to increase IL-10 [41]. In addition, NO is a potent vasodilator [42] and can increase the blood supply to the light illuminated tissue. PBM-mediated vascular regulation increases tissue oxygenation and also allows for greater traffic of immune cells, which may contribute to the promotion of wound repair and regeneration [34].

Moreover, PBM, when delivered appropriately, reduces pain and improves function [19, 30–32]. In addition, in vivo studies show that PBM is neuroprotective and may benefit neurodegenerative diseases and neurotrauma [33, 34]. Analgesic effects are probably induced by additional mechanisms rather than by the increased ATP/reduced oxidative stress model. PBM with a relatively high power density (> 300 mW/cm^2), when absorbed by nociceptors, has an inhibitory effect on A and C neuronal pain fibers. This slows neural conduction velocity, reduces amplitude of compound action potentials, and suppresses neurogenic inflammation [19].

Preliminary studies suggest that multiple conditions that may play a role in the pathogenesis of RT- and CRT-induced complications in patients treated for HNC (e.g., ulceration, inflammation, lymphedema, pain, fibrosis, neurological and muscular injury) may be modulated by PBM. For example, in an animal model of OM, it was demonstrated that PBM decreased COX-2 expression [43] and decreased the number of neutrophils in the inflammatory infiltrate [44]. Moreover, in the chronic sequelae of RT and CRT, an excessive fibroblastic response is hypothesized to be related to acute oxidative injury, with resulting cell damage, ischemia, and an ongoing inflammatory response resulting in fibrosis [45]. The critical difference between normal wound healing and fibrosis development appears to be, that in fibrosis, signaling pathways escape normal cellular regulation [46]. Reduction of fibrosis could be mediated by the beneficial effects of PBM on the oxidant/antioxidant balance [47], downregulation of TGF-β, and inhibition of excessive fibroblast proliferation [48].

Although most studies have demonstrated efficacy in management of both acutely and chronically affected tissues, not all PBM investigations have yielded positive outcomes. As discussed below, these divergent results may be attributed to several factors, most importantly dosimetry. Clearly, more investigation at the molecular, cellular, and tissue level is needed to fully understand the complexity of PBM function.

PBM parameters

PBM parameters have been mostly reported within the red and NIR wavelength range of 600–1000 nm, with a power density of between 5 and 150 mW/cm^2 and are typically applied for 30–60 s per point. The therapeutic effect is dictated by the energy density measured in joule per centimeter squared.

Commonly reported PBM devices include helium-neon (HeNe) gas laser, gallium–arsenide (GaAs), neodymium-doped yttrium aluminum garnet (Nd:YAG), gallium aluminum arsenide (GaAlAs), indium gallium aluminum phosphide (InGaAlP) diode lasers, non-thermal, non-ablative carbon dioxide (CO_2) lasers, LED arrays, and visible light.

The PBM effects on the exposed tissues depend on the following: cell type, redox state of the cell, irradiation parameters (including wavelength, power density), and time of exposure [23, 49]. A biphasic dose response has been shown, which underlines that there are optimal irradiation and dose parameters, although these will likely vary according to underlying pathology (cellular layers and depth from the surface of application), mucosal surface or skin, and individual patient-associated factors [50]. Bearing in mind, dosage lower than the optimal value may have a diminished effect, while doses higher than optimal can have negative therapeutic outcomes [34, 49].

Thus, for PBM to be effective, the irradiation parameters, including the energy delivered, power density, pulse structure, delivery to the appropriate anatomical location (operator-dependent effect), and appropriate treatment timing and repetition, need to be within the biostimulatory dose windows [22, 34, 49, 51, 52].

Titrating adequate doses and defining the other required PBM parameters according to evidence gathered in a systematic manner for each indication is a prerequisite for treatment success. Without standardization in beam measurement, dose calculation, and the correct reporting of these parameters, studies will not be reproducible, and outcomes will not be consistent. A common misconception is that wavelength and energy (in J) or energy density (J/cm^2) are all that is necessary in order to replicate a successful treatment and that the original power, power density, and duration parameters do not matter [53, 54].

A checklist to help researchers understand and report all the necessary parameters for a reproducible scientific study has been developed (Table 1) [54]. PBM devices are manufactured depending on “class” of laser device with multiple options to control the above dosimetry. However, it is not uncommon to find discrepancies between the specifications provided by a device manufacturer and the actual performance of the device [55]. Therefore, device maintenance including power measurements should be carried out regularly during research trials and also in clinical practice.

Potential effects of PBM on tumor

The first prerequisites for any potential agent to be used to prevent cancer regimen-related complications are that it does not adversely affect tumor risk, tumor behavior, or tumor response to treatment.

Given the breadth of PBM’s biology, there exists a significant opportunity and it is imperative to establish its tumor-related neutrality, or even the possibility that PBM might provide an adjunctive therapy when used with conventional modes of anti-cancer treatment. As noted below, currently, there are more questions than answers. Although it seems highly unlikely (both teleologically and based on available data) that PBM in itself poses a carcinogenic threat, its potential to alter established tumor behaviors such as proliferation or invasion may not be trivial [56]. We do know that PBM effectively activates a sweeping range of pathways and mediators which have been implicated in tumor conduct. Thus, opportunities for pre-clinical and clinical research abound.

Molecular biology

Significant progress has been made in the past decade in our understanding of the molecular biology which drives head and neck squamous cell carcinoma (SCC) and the mechanisms of action of PBM.

PI3K/AKT/mTOR signaling pathway

Activation of the PI3K/AKT/mTOR pathway is associated with many of the activities that may be associated with PBM's favorable impact on wound healing: cell survival, migration, proliferation, and angiogenesis. Yet PI3K/AKT/mTOR signaling is also among commonly dysregulated pathways associated with cancer, including head and neck SCC [57], and its activation has been reported to promote the acquisition of epithelial-mesenchymal transition, cancer stem cell phenotypes, and cancer radioresistance [58]. Conversely, inhibition of the pathway has been viewed as a potential strategy to increase radiation sensitivity of tumor cells [59]. Recently reported data suggest that the migration of oral keratinocytes to occur following PBM is attributable to activation of the AKT/mTOR signaling pathway [60]. Consequently, the observation reported by Sperandio et al. [61] that PBM modified the expression of proteins related to the progression and invasion of oral cancer cell lines suggests that PBM activation of the AKT/mTOR signaling pathway may be undesirable. The lack of data from in vivo models or patients leaves open the question on the breadth of PBM effects on malignant cells and non-malignant tissue. For example, assuming AKT/mTOR is activated by PBM, would tumor tissue be affected if it was distant from the site of application, i.e. treating the mouth for OM in an individual being treated for a hypopharyngeal cancer?

TGF-β signaling pathway

TGF-β has potentially contradictory roles relative to tumor behavior [62]. While its tumor suppressive effects are notable in the early stages of carcinogenesis, it may promote growth and spread of established tumors. Through serine/threonine kinases and Smad effectors, TGF-β can act as a tumor suppressor by inhibiting proliferation and inducing apoptosis [63]. Conversely, it may be overproduced by human tumors and is associated with induction of epithelial-mesenchymal transition, the prelude to tumor invasiveness, angiogenesis, suppression of elements of immune surveillance, and recruitment of signaling pathways that may facilitate metastases [64]. Additionally, it appears that TGF-β1 signaling may enhance tumor progression by altering the surrounding stroma through Smad signaling [65]. Thus, the observation that PBM stimulates TGF-β/Smad signaling pathway [66] could be viewed as a double-edge sword depending on when and what tissue was exposed [67].

MAPK pathways

Mitogen-activated protein kinase (MAPK) pathways play a significant role in cancer [68]. Among the MAPK pathways, perhaps the best studied relative to cancer is the ERK pathway. ERK signaling is associated with a number of tumor behaviors. Of relevance to HNC is a correlation of its expression with increased epithelial growth factor receptor (EGFR) [69]. The ERK pathway also impacts vascular epithelial growth factor (VEGF) expression and its consequent angiogenesis. While angiogenesis may be desirable from a

wound healing perspective, the finding that PBM stimulates EGFR and VEGF production through ERK signaling may be a concern in a tumor environment [70, 71].

Heat shock proteins and microRNAs

The robust biological effects of PBM are borne out by the observations of its ability to stimulate a range of biological processes including upregulation of heat shock proteins (HSP) [72] and microRNAs [73]. Relative to the current discussion, HSP is essential for cancer survival and has been identified as a potential target for anti-cancer therapy.

While the number of miRNAs that are upregulated following PBM is substantial, of particular note is the finding that mi126 is among the list as endogenous mi126 has been reported to be associated with metastatic progression [74].

Molecular pathways with a potentially favorable effect

While the information above raises questions about possible undesirable effects of PBM on tumor progression and response to anti-cancer treatment, some observations suggest that PBM might favorably impact tumor behavior through its effects on vimentin expression, MyD88-dependent signaling, reduction in TLR-4, and downregulation of NF-κB [75]. Furthermore, upregulation of ATP signaling by PBM may promote apoptosis, as well as differentiation of tumor cells, thereby slowing tumor proliferation [30, 76].

PBM effects on tumor cell lines

The effects of PBM on cell proliferation and differentiation have been investigated in vitro using malignant cell lines, which have generated conflicting data across a range of different tumor cell lines and PBM parameters [77–81]. For example, Kreisler and coworkers reported proliferation of laryngeal carcinoma cells after 809 nm GaAIAs laser irradiation at energy densities between 1.96 and 7.84 J/cm^2 [78]. Werneck and coworkers also found increased cell proliferation of HEp2 carcinoma cells after PBM exposure at different wavelengths (685 and 830 nm) and doses [82]. In a study comparing PBM administered to normal osteoblasts and to osteosarcoma cells with a range of different wavelengths and doses, only 10 J/cm^2 from an 830 nm laser was able to enhance osteoblast proliferation, whereas energy densities of 1, 5, and 10 J/cm^2 from a 780-nm laser decreased proliferation. Osteosarcoma cells were unaffected by 830 nm laser irradiation, whereas 670 nm laser had a mild proliferative effect [83]. An in vitro study compared the effects of different doses of PBM at various wavelengths on human breast carcinoma and melanoma cell lines [84]. Although certain doses of PBM increased breast carcinoma cell proliferation, multiple exposures had either no effect or showed negative dose response relationships. PBM (wavelength 660 nm) administered in low doses (1 J/cm^2) increased in vitro proliferation and potentially increased invasive potential of tongue SCC cells [56]. Similarly, another in vitro study suggested that PBM (660 or 780 nm, 40 mW, 2.05, 3.07, or 6.15 J/cm^2) may stimulate oral dysplastic and cancer cell lines [61].

In contrast, a decreased mitotic rate was found in gingival SCC after PBM at 805 nm and energy density of 4 and 20 J/cm^2 [80], whereas no effect on cell proliferation or protein expression of osteosarcoma cells was found when PBM was administered with a wavelength

of 830 nm [85]. PBM (808 nm; 5.85 and 7.8 J/cm^2) had an inhibitory effect on the proliferation of a human hepatoma cell line [86], and Sroka et al. [87] reported that glioblastoma/astrocytoma cells exhibited a slightly decreased mitotic rate after PBM at 805 nm and 5–20 J/cm^2. Similarly, 808-nm laser irradiation with an energy density of more than 5 J/cm^2 inhibited cell proliferation of glioblastoma cells in vitro [88]. Moreover, Al Watban et al. [89] observed growth inhibition of cancer cell lines at relatively high cumulative PBM doses. This prompted Crous and Abrahamse [90] to hypothesize that PBM may have a therapeutic potential in lung cancer.

Protective effects of PBM against cytotoxic therapy

There are no data to suggest that PBM may protect cancer cells against the cytotoxic effects of RT. On the contrary, Schartinger et al. [91] observed a pro-apoptotic effect of PBM in head and neck SCC cells, whereas no anti-apoptotic effects occurred that might promote tumor cell resistance to cancer therapy. Increased apoptosis of human osteosarcoma cells was also induced by the administration of NIR (810 nm, continuous wave, 20 mW/cm^2, 1.5 J/cm^2) prior to NPe6-mediated photodynamic therapy as a result of increased cellular ATP and a higher uptake of the photosensitizer [92]. Recently, it was reported that PBM administered to normal human lymphoblasts and leukemia cells prior to RT, resulted in a differential response of normal versus malignant cells suggesting that PBM does not confer protection and may even sensitize cancer cells to RT-induced killing [93]. Nevertheless, in vivo and clinical studies are warranted before firm conclusions can be drawn.

Carcinogenic effects of PBM on normal cells

It seems unlikely that PBM has carcinogenic effects on normal cells. The non-ionizing wavelengths of the red and NIR spectrum used in PBM are far longer than the safety limit of 320 nm for DNA damage [94]. No signs of malignant transformation in non-malignant epithelial cells and fibroblasts were observed following exposure to PBM with a wavelength of 660 nm, 350 mW for 15 min during 3 consecutive days [91]. In addition, no malignant transformation of normal breast epithelial cells was detected in an in vitro study comparing the effects of different doses and wavelengths of PBM during multiple exposures [84].

Data derived from in vivo and clinical studies

PBM (660 nm, 30 mW, 424 mW/cm^2, 56.4 J/cm^2, 133 s, 4 J), applied to chemically induced SCC in hamster cheek pouch tissue, increased tumor growth [95]. PBM at a dose of 150 J/cm^2 appeared safe, with only minor effects on B16F10 melanoma cell proliferation in vitro, and had no significant effect on tumor growth in vivo. Only a high power density (2.5 W/cm^2) combined with a very high dose of 1050 J/cm^2 could induce melanoma tumor growth in vivo [96]. In a mouse model to study PBM effects on UV-induced skin tumors, the experimental mice received full body 670 nm PBM delivered twice a day at 5 J/cm^2 for 37 days, whereas controls received sham PBM [97]. No enhanced tumor growth was observed, whereas there was a small but significant reduction in tumor area in the PBM group, potentially related to a local photodynamic effect or PBM-induced antitumor immune activity.

Schaffer et al. [98] observed that PBM increased the locoregional blood flow that contributed to better local oxygenation and hypothesized that PBM applied shortly before cancer treatment might enhance the effect of ionizing RT and local delivery of chemotherapy. A recent randomized controlled trial in which PBM was administered for prevention of OM during CRT in HNC patients (diagnosed with SCC of the nasopharynx, oropharynx, or hypopharynx) reported that at a median follow-up of 18 months (range 10–48 months), patients treated with PBM had better locoregional disease control and improved progression-free or overall survival [99].

Current evidence suggests that PBM in the red or NIR spectrum, with an energy density of 1–6 J/cm^2 is safe and effective. However, as with drug-based therapies for comparable indications, disciplined follow-up studies in which subject cohorts large enough to represent the HNC tumor population with respect to gender, tobacco and alcohol use, human papilloma virus (HPV) status, primary stage, tumor therapy, and variations in PBM dose and fields are needed to definitely conclude that PBM fails to negatively impact survival and progression-free survival.

Discussion and concluding remarks

PBM mechanisms have not been fully elucidated, but based on its recognized therapeutic effects, PBM may have utility in a broad range of oral, oropharyngeal, facial, exocrine glands, and neck complications of HNC treatment.

Titrating adequate doses and defining the other required PBM parameters according to evidence gathered in a systematic way for each indication is a prerequisite for a successful use of this technique. Without standardization in beam measurement, dose calculation, and the correct reporting of these parameters, studies will not be reproducible, and outcomes will not be consistent.

There are no known significant adverse side effects for PBM (administered with parameters discussed in more detail in part 2) in HNC patients. However, the potential effect on residual and new dysplastic and malignant cells has not been definitively resolved. Virtually, all studies have focused on cell-based assays rather than conventional xenograft or orthotopic animal models. And the results of in vitro investigations have been largely dependent on the experimental design and selection of target cells.

The lack of consistent findings and/or the latitude of interpretation of the clinical significance of molecular biology findings hamper meaningful conclusions. Continuing research addressing the molecular pathways affected by PBM is necessary.

It seems unlikely that PBM has carcinogenic effects on normal cells or protects to cytotoxic effects of RT; there is even some evidence suggesting that PBM may enhance treatment response.

Studies indicate that different tumor cells have distinct responses to specific PBM parameters and doses. In part, these differences may be also explained by variations in the cellular microenvironment, since these have been shown to affect cellular signal transduction

pathways to PBM exposure [100]. The microenvironment of tumor cells varies among in vitro studies and differs significantly from that found in animal models. Moreover, this difference implies that the potential of PBM to enhance proliferation of tumor cells in vitro does not necessarily translate into harmful effects of PBM in cancer patients. However, more research is necessary and vigilance remains warranted to detect any potential adverse effects of PBM on cancer treatment outcomes and survival [101].

In the part 2 of this paper, we will identify acute and chronic complications associated with HNC therapy and review the literature relevant to the potential use of PBM for the management of these complications. PBM irradiation and dosimetric ranges, which are potentially effective for these complications, will be proposed. These parameters are intended to provide guidance for well-designed future studies.

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Table 1

Photobiomodulation (PBM) parameters to be reported in clinical studies. Adapted from [54]

Category	Parameter	Unit	Explanation
Irradiation parameters	Wavelength	Nanometer (nm)	Light is packets of electromagnetic energy called photons that sometimes behave like particles but also have a wave-like property. Wavelength determines which chromophores will absorb the light. Light is visible in the 400–700-nm range. The energy of each photon is greater at short wavelengths than longer wavelengths; e.g., red light is ~2 elektronvolt (ev) per photon and blue light is ~3 ev.
	Power	Watt (W)	The number of photons per second. The higher the power the more photons emitted every second.
	Beam area	Centimeter squared (cm^2)	The surface area of the beam on the patient. Also known as spot size. This is not always easy to determine because laser beams are usually more intense in the middle then fade towards the edge (Gaussian distribution) so it is hard to define where the exact edge of the beam is without special instruments. Many research authors do not report this parameter, let alone report it correctly.
	Aperture size	Centimeter squared (cm^2)	The area of the light source tip. This is not necessarily identical as the beam area. The difference between the aperture size and beam area will be determined by the beam divergence and distance of the light source tip from the tissue.
	Irradiance (power density, or intensity)	Watts per centimeter squared (W/cm^2)	Power (W) ÷ beam area (cm^2). More irradiance could allow less treatment time; however, many studies have shown that if the irradiance is too high, treatment can be less effective even if the same total dose is delivered. The treatment guidelines suggest the safe and effective irradiance ranges.
	(Radiant) Energy	Joules (J)	Power (W) × time (s). More power could mean less treatment time; however, many studies have shown that too much power is less effective even if the same total energy is delivered. The treatment guidelines suggest the safe and effective energy ranges.
	Time	Second (s)	How long each treatment is applied at each location.
	Dosage (fluence or energy density)	Joules per centimeter squared (J/cm^2)	Energy (J) ÷ beam area (cm^2), or power (W) ÷ beam area (cm^2) × time (s). Different outcomes can be obtained if the total dosage is delivered with high energy and short time or low energy and long time.
	Operating mode	Continuous wave (CW), pulsed	The continuity of the production of the output beam may be continuous or pulsed. There are several types of pulsed beam.
	Pulse structure	Second (s)	The durations of the pulse being on or off.
Treatment parameters	Physical relationship to the organ		Applicable when there is more than one way to approach the organ. For example, intra-oral device versus extra-oral device.
	Timing		Time of the treatment session relative to the cancer treatment.
	Treatment schedule		The frequency of treatments per day/week and the total number of treatments.
	Anatomical location		The anatomical site that was exposed to the light beam. If multiple locations were treated, all need to be described.