Title: 2015-170: A Phase II Prospective Trial of Low-Level Laser Therapy for Prevention of Oral Mucositis in Patients Receiving Chemotherapy and Radiation for Head and Neck Cancer

StudyCenter:
Karmanos Cancer Center
4100 John R
Detroit, Michigan 48201

PrincipalInvestigator:
Harry Kim, M.D.
Associate Professor and Service Chief
Division of Radiation Oncology
Department of Oncology
Barbara A. Karmanos Cancer Center
Wayne State University School of Medicine
4201 St Antoine UHC-1D
Detroit MI 48201
kimh@karmanos.org
Phone: 313-576-9543
Fax: 313-576-9625

Co-investigators:
Mark Zaki, MD
Resident, Radiation Oncology
Karmanos Cancer Center
Wayne State University School of Medicine
4201 St Antoine UHC-1D
Detroit MI 48201
mazaki@med.wayne.edu
Phone: 313-576-9632
Fax: 313-576-9625

Pam Laszewski RN, OCN
Clinical Leader, Radiation Oncology
Karmanos Cancer Center
4100 John R
Mail code: GE00R0
Detroit, MI 48201
laszewsk@karmanos.org
Phone: 313-576-9563
Fax: 313-576-9639

Statistician:
Greg Dyson, PhD
Biostatistician
Assistant Professor, Biostatistics Core
Karmanos Cancer Institute
Wayne State University
dysong@karmanos.org
Phone: 313-576-8654

StudyCoordinator:
Ted Chaperon
Study Coordinator
Karmanos Cancer Institute
Clinical Trials Office
4100 John R Mailcode: GE00CT
Detroit, MI 48201
Phone: (313) 576-9383
Fax: (313) 576-8364

CurrentVersionDate: 07/20/2016
Previous Version Dates: 12/03/2015
04/12/2016

TableofContents

StudySchema

A phase II, single-arm trial to examine the efficacy of prophylactic low-level laser therapy (LLLT) to reduce the incidence of oral mucositis and adverse events in patients receiving combined modality therapy consisting of chemotherapy and radiation therapy for head and neck cancer.

Patients meeting the eligibility criteria will be enrolled to receive prophylactic LLLT in addition to standard of care measures for oral mucositis or other toxicity of therapy. The radiation and chemotherapy dose, schedule, modality, technique, and any required adjustments will not be influenced by this protocol and will follow standard existing institutional practices.

Patients will receive LLLT three times per week concurrently with chemoradiotherapy. LLLT may be delivered either immediately prior to or after the patient's daily fraction of radiotherapy. Patients will be treated extra-orally with a THOR® LED cluster for one minute along the buccal mucosa on each side and intraorally for one minute to the tongue and soft palate. During each LLLT treatment session a thorough oral exam will be performed to identify any areas of mucositis. If the patient should develop intraoral lesions they will be targeted directly with the intraoral probe for one minute to each site of mucositis. The laser settings to be used are as follows: frequency 2.5 Hz; wavelength 660 nm; and power 75 mW, for an energy of 4.5 J.

Patients will be evaluated prior to therapy, weekly during therapy, two weeks after the completion of therapy, and three months after the completion of therapy. During each assessment, the following toxicities will be assessed: pain, mucositis, dysphagia, xerostomia, dysgeusia, dermatitis, trismus, and quality of life.

Previous studies indicate that approximately 40% of patients will experience severe mucositis with radiation and concurrent chemotherapy. The hypothesis in this trial is that the addition of LLLT to this treatment regimen will decrease the rate of severe acute OM to 20%. We plan to enroll 25 patients at our institution in 12 months after the trial opens. The same protocol will be opened separately at the University of Pittsburgh Medical Center (UPMC), where an additional 25 patients will be enrolled. A Data Use Agreement will allow combination of the data for a total of 50 patients to be analyzed.

1.0 Objectives:

1.1 PrimaryObjective

Our primary objective is to determine the ability of low-level laser therapy (LLLT) to reduce the rates of severe oral mucositis in patients receiving radiation with concurrent chemotherapy for head and neck cancer (HNC).

1.2 SecondaryObjectives

1. To establish the time to onset of severe oral mucositis following the initiation of radiotherapy with LLLT.
2. To determine the incidence of pain, dysphagia, xerostomia, dysgeusia, trismus, radiodermatitis, and OM-related QOL (via FACT-H&N score) with LLLT.
3. To evaluate the mean cumulative radiation dose at time of onset of severe oral mucositis with LLLT.
4. Determine the duration of oral mucositis.
5. Record the amount of narcotic analgesia use during treatment.
6. Evaluate the number of breaks in chemoradiotherapy with LLLT use.
7. Determine the proportion of patients who require feeding tube placement during treatment.

2.0 Introduction

2.1 DiseaseOverview

Combined modality therapy with chemotherapy and radiation is a commonly employed treatment approach for patients with various types of HNC [1]. Despite the overall safety and efficacy of this treatment modality, side effects exist, including acute chemoradiation-induced pain, dermatitis, xerostomia, dysgeusia, dysphagia, odynophagia, and oral mucositis. In fact, a majority of patients treated with this modality will experience some degree of oral mucositis (OM) [2]. OM can affect many oral functions including mastication and swallowing which may lead to dehydration, renal failure and necessitate the placement and use of a feeding tube and negatively impact and patient's quality of life (QOL). Severe OM can also predispose a patient to increased risk of infections requiring hospitalization and increased cost of treatment [3]. The severity of these reactions can be so severe that patients who experience treatment-related mucositis are less likely to complete the planned course of therapy without unplanned interruptions in therapy. Previous studies provide evidence that unplanned breaks in radiotherapy for HNC result in worse tumor control [4]. Furthermore, adverse events can increase the cost of healthcare by resulting in preventable hospital admissions for intravenous hydration and nutritional support and procedures including feeding tube placement. In fact, OM has

been shown to be associated with an incremental cost of $1,700 - $6,000 per patient, depending on the grade [5].

Despite multiple clinical trials, no single treatment has been proven to be effective in substantially reducing incidence or severity of chemoradiation induced oral mucositis. The current standard practice for the management of OM is symptom management and supportive care with narcotic pain medications and anesthetic mouth rinses and nutritional support with supplementation either by mouth or feeding tube.

2.2 ProductBackground

Photomedicine utilizing low level laser (or "light" as light emitting diode sources are increasingly being used in place of lasers) therapy (LLLT) has been investigated as a novel therapeutic approach since the 1960s. LLLT is a safe, low-intensity form of light therapy. LLLT employs visible (generally red) or near-infrared light generated from a laser or light emitting diode (LED) [6]. Therapy with LLLT has been shown to relieve pain, reduce inflammation, and improve tissue repair. LLLT does not function through ablative or thermal mechanisms, but rather a photochemical effect comparable to photosynthesis in plants whereby the light is absorbed and exerts a chemical change [6].

LLLT was first completely limited to treatment with laser sources, such as the helium neon (HeNe) or indium phosphide, gallium and aluminum diode (InGaAIP) lasers. The non-coherent light produced by light emitting diode (LED) devices has the same biological properties and clinical effectiveness as coherent light produced by lasers, with the advantages of LED technology being that it is significantly less expensive and can be arranged in arrays permitting greater surface area exposure and subsequent shorter overall treatment times. Furthermore, LED-based LLLT applied extraorally has good penetration through skin and soft tissue to the oral mucosa [7]

2.3 ProductMechanismofAction

The mechanism of action no LLLT is rooted in photochemistrisy. Light photons must be absorbed by molecular photoacceptors or chromophores for photochemistry to occur [8]. The cellular mechanism of LLLT has been attributed to the absorption of monochromatic visible and near infrared (NIR) radiation by the cellular respiratory chain [9]. Phototherapy is characterized by its ability to induce photobiological processes in cells. Mitochondria play a crucial role in cellular metabolism and the generation of energy in the form of adenosine triphosphate (ATP) through oxidative phosphorylation. Mitochondria have been studied as the main target of phototherapy. Cytochrome c oxidase is the proposed photoacceptor for the red-NIR light range in mammalian cells, as absorption spectra for light were found to be similar to the absorption spectra of cytochrome c oxidase [10]. LLLT to isolated mitochondria increased ATP synthesis, RNA and protein synthesis, and enhanced synthesis of NADH and ATP [6]. In stressed tissues, mitochondria make nitric oxide that competes with oxygen in the oxidative phosphorylation chain. This in turn decreases ATP synthesis and can increase production

of reactive oxygen species (ROS), which are small molecules that are highly reactive with proteins, nucleic acids, and lipids. ROS are potentially harmful to intracellular elements and their formation triggers cellular sensors that can engage signaling pathways involved in gene transcription (such as nuclear factor κB (NF-κB). While the exact mechanism of action is unknown, LLLT has been shown to interact with cytochrome c oxidase in mitochondria to release nitric oxide, facilitating oxidative phosphorylation. This increases ATP production and stimulates downstream signals to produce antioxidants and growth factors for cellular repair and proliferation. As a result, LLLT has been shown to decrease pain and inflammation and promote wound healing and tissue repair.

2.4 ProductEfficacy

LLLT is a non-invasive technique which has been examined for the prevention and treatment of radiotherapy-induced OM. Multiple randomized trials have shown a reduction in the rates of OM and pain with the use of LLLT [11-20]. A list of trials examining the impact of LLLT for OM prevention in patients with HNC is given in table 1.

Furthermore, a systematic review and meta-analysis of eleven randomized placebo-controlled trials of LLLT use during chemotherapy or radiation therapy in HNC patients was performed [21]. This found a relative risk for developing OM was significantly ($p=0.02$) reduced after LLLT compared with placebo. The number of days with OM grade 2 or worse was also significantly reduced after LLLT to 4.38 days less than placebo. Likewise, OM severity was reduced after LLLT compared with placebo. All studies in this meta-analysis recorded possible adverse effects of LLLT therapy, but there were no differences from treatment with placebo. Evidence from these small, randomized controlled trials shows a significant reduction in incidence and severity of OM for HNC patients.

Additionally, the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) Clinical Practice Guidelines for Mucositis recommends in favor of LLLT for the prevention of OM in patients receiving high-dose chemotherapy for hematopoietic stem cell transplants with or without total body irradiation and a suggestion for LLLT in the prevention of OM in patients receiving RT for HNC [22]. No guideline was issued for patients receiving concurrent chemotherapy and radiation therapy for HNC due to lack of high-level evidence. The European Society for Medical Oncology (ESMO) clinical practice guidelines for the management of oral and gastrointestinal mucositis also advises the use of LLLT to reduce the incidence of oral mucositis and its associated pain, in patients receiving high-dose chemotherapy or chemoradiotherapy before hematopoietic stem cell transplant [23].

Table 1. LLLT trials for oral mucositis prevention

Reference	Population	Methods	Treatment	Results	Comments
Antunes et al Radiother Oncol 2013[11]	HNC (n=94) Brazil, 2007 2010	Phase III, randomized placebo controlled trial	Concurrent Chemoradiotherapy (1) Placebo~ (2) LLLT daily prior to each RT fraction Chemo: cisplatin 100 mg/m^2 q3weeks RT: 70.2 Gy LLLT: InGaAlP, 660 nm, 100mW, 1-4J/cm^2	Grade 3 4 mucositis (WHO): 40.5% vs. 6.4% Relative risk: 0.16 (0.05 0.5)	Improved QOL for pain, swallowing and difficulty with eating
Arora et al Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2008[13]	Oral cancer (n=50) India, 2005-2006	Phase III, randomized controlled trial	Radiation (1) Topical anesthetic, saline washes~ (2) LLLT daily prior to RT RT: 66 Gy LLLT: He Ne, 632.8 nm, 10mW, 1.8J/cm^2	Grade 3-4 mucositis (EORTC/RTOG) 53.9% vs. 18.2% at 3 weeks (p=0.019)	Functional impairment Scale maximum score: Oral alimentation not possible: 31% vs. 0%
Bensadoun et al Support Care Center 1999[14]	HNC (n=30) France, 1994-1998	Phase III, randomized placebo controlled trial	Radiation (1) Placebo~ (2) LLLT prior to each RT fraction RT: 65 Gy LLLT: He Ne, 632.8 nm, 60mW, 2J/cm^2	Grade 3 mucositis (WHO): 35.2% vs. 7.6% (p<0.01) Severe pain: 23.8% vs. 1.9% (p<0.05)	
Gautam et al Radiother Oncol 2012[16]	HNC (n=221) India, 2009-2011	Phase III, randomized placebo controlled trial	Concurrent Chemoradiotherapy (1) Sham treatment~ (2) LLLT 5x/week, prior to or following RT Chemo: cisplatin 100 mg/m^2 q3weeks RT: 66 Gy LLLT: He Ne, 632.8 nm, 24mW, 3J/point	Grade ≥3 mucositis (EORTC/RTOG): 70% vs. 23.4% (p < 0.0001)	Pain scores plateaued after week 4 in LLLT arm and continued to increase in placebo arm Lower dysphagia in LLLT arm
Zanin et al Photomed Laser Surg 2010[18]	HNC (n=72) Brazil	Phase III, randomized controlled trial	Concurrent Chemoradiotherapy (1) No treatment~ (2) LLLT 2x/week, prior to or following RT Chemo: cisplatin~70 mg/m^2 weekly RT: 1.8 Gy daily fractions LLLT: He Ne, 660 nm, 30mW, 2J/cm^2	Mucositis (NCI) significantly lower in LLLT group from week 1 to week 4 (p=0.001), but remained stable until week 7 (p=0.68)	LLLT delayed onset of oral mucositis
Lima et al, Braz Dent J 2010[17]	HNC (n=25) Brazil, 2005	Prospective, non-randomized study	RT ± chemotherapy (1) Sucrose and aluminum hydroxide suspension~ (2) LLLT daily prior to each RT fraction Chemo: cisplatin 100mg/m^2 q3weeks RT: 40 70 Gy LLLT: 830 nm, 60 mW, 12.4J/cm^2	Grade 3 mucositis (OTS Scale) OM 50% vs. 33% (p=0.06)	Significant decrease in pain with LLLT (p=0.036)

HNC; head and neck cancer. LLLT; low-level laser therapy. RT; Radiation. Gy; Gray. InGaAlP; indium phosphide, gallium and aluminum diode. nm; nanometer. mW; milliwatts. J; Joules. WHO; World Health Organization. QOL; Quality of Life. He-Ne; Helium-Neon. EORTC; European Organisation for Research and Treatment of Cancer. RTOG; Radiation Therapy Oncology Group. NCI; National Cancer Institute.

2.5 ProductSafety

Lasers used for LLLT are categorized as Class 3b. Class 3b lasers emit 5mW to 500mW lasers, with some emitting infrared light below 5mW. A class 3b laser may be hazardous under direct and specular viewing conditions, but is not a fire hazard. The patient and LLLT operator require use of protective eyewear. The LLLT system is equipped with a key switch and a safety interlock. The THOR® Laser system (THOR Photomedicine Ltd, Chesham, UK) that will be used to deliver LLLT in this protocol is an FDA-approved medical device (510(K) number K030226).

There has been no reported toxicity in any of the studies of LLLT for the prevention and/ or management of oral mucositis. In the limited number of studies evaluating extraoral LLLT, there has similarly been no reported cutaneous or oral toxicity.

2.6 RationalefortheStudy

Previous phase III trials conducted in other countries, primarily Brazil [11], France [14], and India [16], have shown a significant improvement in OM with LLLT. However, no U.S. trials have been reported. The rationale for this phase II trial is to validate the results from international trials in a U.S. cohort of patients. Therefore, our goal is to evaluate the efficacy of LLLT in reducing treatment related toxicities including OM, pain, xerostomia, dysgeusia, and dysphagia and improving OM-related QOL in patients undergoing radiation with chemotherapy for HNC. To accomplish our goal, we propose a prospective, single-arm, phase II trial with the aim of improving health-care quality and reducing the incidence of treatment-related toxicity as compared to historical controls. The same protocol will be opened separately at the University of Pittsburgh Medical Center (UPMC). A Data Use Agreement will allow for a combination of the data from both centers to be analyzed.

3.0SelectionandWithdrawalofSubjects

3.1 StudyDesign

This is a phase II prospective, single-arm, open label trial testing the efficacy of LLLT in prevention of oral mucositis for HNC patients treated with chemoradiotherapy. Primary endpoints are the incidence of severe (assessed separately as CTCAE v. 4.0 grade 3-5 or WHO grade 3-4) OM in patients receiving a cumulative radiation dose of at least 5000 cGy. Secondary endpoints include the time onset to severe OM, mean cumulative radiation dose at the time of OM, duration of OM, the incidence of pain, dysphagia, xerostomia, dysgeusia, trismus, radiodermatitis, and QOL.

All toxicities will be graded by NCI CTCAE v. 4.0. In addition, oral mucositis will also be graded by WHO mucositis grading scale. Dysphagia will also be graded by a dietary assessment. Trismus will be assessed by measurments of the interincisal distance. QOL will be measured by the FACT-H&N assessment.

Previous studies (detailed in Section 2.2, Table 1) indicate that approximately 40% of patients will experience severe OM with radiation and concurrent chemotherapy. The hypothesis in this trial is that the addition of LLLT to this treatment regimen will decrease the rate of severe acute OM to 20%. We plan to enroll 25 patients at our institution in 12 months after the trial opens. The same protocol will be opened separately at the University of Pittsburgh Medical Center (UPMC), where an additional 25 patients will be enrolled. A Data Use Agreement will allow combination of the data for a total of 50 patients to be analyzed.

3.2 PatientSelection

InclusionCriteria:

1. Willing and able to understand and sign informed consent form approved by the IRB.
2. Males or females greater than or equal to 18 years old.
3. Biopsy-proven HNC including cancers of the nasopharynx, oropharynx, larynx, hypopharynx, or HNC of unknown primary origin amenable to therapy with radiation and concurrent chemotherapy.
4. Patients who are planned to receive definitive or adjuvant radiotherapy with concurrent platinum-based chemotherapy.
5. Patients whose clinical treatment plans include a continuous course of external beam radiotherapy by intensity-modulated radiation therapy (IMRT) and/or image-guided radiation therapy (IGRT), given as a cumulative dose of 5000 – 7000 cGy in single daily fractions of 180 - 200 cGy, combined with a concurrent course of weekly or tri-weekly cisplatin or carboplatin chemotherapy.
6. Karnofsky performance status score >60.
7. Female patients of child-bearing potential must have a negative pregnancy test prior to enrollment.

ExclusionCriteria:

1. Patient has evidence of current mucositis, mucosal ulceration, or unhealed surgical wounds from surgical resection or biopsy.
2. Prior radiation to the head and neck.
3. Patients with gross tumor involvement of the oral cavity or oral mucosa.
4. Patient planned to receive altered fractionation radiotherapy or multiple fractions per day
5. Patient is using a pre-existing feeding tube for nutritional support at the time of study entry.
6. Women who are pregnant or breast-feeding.
7. Patient plans to receive concurrent chemotherapy, other than the regimens specified in the inclusion criteria.
8. Patients who have chronic immunosuppression or are on current immunosuppressive therapies.
9. Patients who have a contraindication to radiation therapy.
10. Patients enrolled on another investigational trial for oral mucositis prevention.
11. Life expectancy of less than 3 months.
12. Unable or unwilling to adhere to study-specified procedures.

3.3 WithdrawalofSubjects

Any subject, having previously provided informed consent to participate in the protocol, is free to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the study site. The Investigator or Sponsor may also withdraw the subject at any time in the interest of subject safety. The primary reason for withdrawal must be recorded.

Subject participation may be terminated prior to completion of the clinical study for any of the following reasons:

1. Unacceptable toxicity
2. Death
3. Lack of efficacy
4. Withdrawal by subject
5. Lost to follow-up
6. Non-compliance with study treatment (Subjects who miss >20% of planned LLLT treatments will be considered non-compliant with the protocol)
7. Study physician decision in the best interest of subject safety
8. Pregnancy
9. Major protocol deviation that can affect the safety or efficacy of study population
10. Study terminated
11. Other

4.0 TreatmentMethods

4.1 RadiationTreatment

Prior to treatment, all patients will provide informed written consent for radiation therapy as per existing institutional policy. All patients will undergo a computed tomography (CT) simulation for treatment planning. Radiation therapy will be delivered with an intensity modulated radiation therapy (IMRT) technique and/or image-guided radiation therapy (IGRT). The prescribed course of radiotherapy will not be altered based on this study. Radiotherapy will be delivered 5 days per week, Monday – Friday with one radiation treatment given per day. The planned cumulative dose of radiation will be determined by the treating physician and will range from 5000 – 7000 cGy in 180 - 200 cGy daily fractions over the course of 5-7 weeks. This treatment is not part of the research protocol.

4.1.1 DefinitionofTargetVolumes:

Target volumes will be outlined per institutional practice and not modified based on this protocol. Target volumes are defined as the following:
Gross Tumor Volume (GTV) represents the region judged to contain gross primary tumor or involved node(s) based on clinical and endoscopic examinations, CT scan, and, when applicable, other imaging techniques.

Clinical Target Volume (CTV) is defined as the GTV plus areas considered at risk for containing microscopic disease delineated by the treating physician. The CTV margins can be narrower when GTV is in the proximity of the spinal cord or critical normal tissues.
Planning Target Volume (PTV) represents an additional margin around the CTV to compensate for the variability of treatment set up and internal organ motion.

4.1.2 Definitionof OrgansatRisk:

CT-based planning will be used to identify the target volumes and organs at risk (OARs). OARs will be contoured according to the DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology, and TROG consensus guidelines [24] which are included in table 2 which is provided in appendix 11.4. The dose parameters given to OARs will be recorded (table 3). Dose limits to OARs will be determined by institutional practice and specific dose-constraints will not be required on this protocol. The following radiation doses will be recorded.

Table3.DoseparameterstoOARstoberecorded

Brainstem	Maximum Dose_____	
SpinalCord	Maximum Dose_____	
RightParotid	Mean Dose_____	$V30_{Gy}$_____
LeftParotid	Mean Dose_____	$V30_{Gy}$_____
Parotids(bilateral)	D20cc_____	
SubmandibularGland	Mean Dose_____	
ExtendedOralCavity	Maximum Dose_____	Mean Dose_____
Lips	Maximum Dose_____	Mean Dose_____
BuccalMucosa	Maximum Dose_____	Mean Dose_____
Mandible	Maximum Dose_____	
PharyngealConstrictors	Mean Dose_____	

4.2 Chemotherapy

Prior to treatment, all patients will provide informed written consent for chemotherapy as per existing institutional policy. The prescribed course of chemotherapy will be determined by the managing medical oncologist per institutional practices and will not be altered based on this study. The frequency and dose of chemotherapy will be recorded for each patient on the trial. This treatment is not part of the research protocol.

4.3 Low-LevelLaserTherapy

Treatment will be administered on an outpatient basis. While there are no expected toxicities, potential adverse events will be monitored per Section 7 (Adverse Events and Safety Monitoring). No investigational agents or therapies for the prevention of oral mucositis other than those described in this protocol may be administered.

LLLT will be delivered with the THOR® Laser system (THOR Photomedicine Ltd, Chesham, UK). LLLT will begin on the first or second day of radiotherapy and be delivered three times per week (e.g. Monday, Wednesday, and Friday) until the completion of radiotherapy. A trained radiation oncology nurse or physician will deliver treatment. LLLT may be delivered either immediately prior to or after the patient's daily fraction of radiotherapy. If it is determined that a break in radiotherapy is required for clinical reasons, LLLT will also be held. Patients will be treated extra-orally with a THOR® LED cluster for one minute along the cheek to treat the buccal mucosa on each side and intraorally for one minute to the tongue and soft palate. During each LLLT treatment session a thorough oral exam will be performed to identify any areas of mucositis. If the patient should develop intraoral lesions they will be targeted directly with the intraoral probe for one minute to each site of mucositis.

The laser settings to be used are as follows: frequency 2.5 Hz; wavelength 660 nm; and power 75 mW. The dose per anatomic site treated will be 4.5 J/cm^2. No dose modifications for the LLLT will be made.

The extra-oral probe will be cleaned before and after each use. Prior to each use, the intraoral probe will be covered with a protective dental sleeve. Patients and laser operator will wear THOR® laser safety glasses for the duration of laser therapy.

Treatment dates and sites will be recorded for each patient on the LLLT Treatment Record Form given in the appendix (appendix 11.3). Compliance with therapy will be documented. Subjects who miss >20% of planned LLLT treatments will be considered non-compliant with the protocol. For each treatment session, the dose will be set (timer on control unit) and the patient will be positioned comfortably a chair. The LLLT device will be for a minimum of 3 exposures:

1. Right cheek
2. Left cheek
3. Tongue/Soft palate

The treatment per site will take 60 seconds, for a minimum treatment time of three minutes. If any areas of mucositis are evident on examination at the time of LLLT treatment, each area will be targeted with an intraoral probe for an additional 60 seconds.

There will be no pre- or post-treatment measures/precautions.

4.4 Othertreatments

Subjects that develop symptomatic mucositis will be managed as necessary according to standard standard of care hospital protocol for oral mucositis in addition to LLLT. This may include topical creams, pain medications, anesthetic mouth rinses, mouth coatings, and nutritional support with supplementation either by mouth or feeding tube, without the use of specific investigational, restricted agents. No standard treatment will be denied to a patient on this protocol.

5.0 Follow-upandAssessments

5.1 FollowupSchedule

A general history & physical by a radiation oncologist and/or medical oncologist must be done within 8 weeks prior to registration. Patients will be evaluated for protocol eligibility at the time of initial consultation. At the time of initial evaluation, baseline assessments will be performed. During the course of treatment, each patient will be seen by the supervising physician in clinic for an on-treatment evaluation at least once per week (or at an interval of once per five radiation treatments). Follow-up appointments will be scheduled for two weeks and three months after the completion of therapy.

Table 4. Study Calendar Overview

Screening	Baseline	Treatment Period		Follow-up Period
		Assessments	LLLT Dosing	
Day -1 to Day -28	Study Day 0	Weekly Last day of treatment	3x/week concomitant with chemoradiation	Two weeks Three months

5.2 Follow-upAssessments

During each assessment, the following toxicities will be assessed: pain, OM, dysphagia, xerostomia, dysgeusia, dermatitis, trismus, and QOL.

Mouth pain and throat pain severity will be assessed weekly using a standard 0-10 scale. A record of the amount of analgesic medications required will be required at each visit.

A diet assessment will be performed at weekly on-treatment assessments as follows:

DietAssessment		
Diet1: What has the subject been able to eat within the past 24 hours (mark only one) ☐Solids ☐Liquids ☐Nothing by Mouth If **Solids** is marked above, proceed to next section. If **Liquids** or **Nothingby Mouth** is marked about continue to "Diet 2".	**Diet2:** If the subject has been unable to eat Solid food, mark all the reason(s) why (mark all that apply) ☐Nausea/Vomiting ☐Oral discomfort ☐Loss of appetite ☐Dry mouth ☐Throat discomfort ☐No teeth ☐Difficulty Swallowing ☐Other_____ If **Oraldiscomfort** is marked above, proceed to the next section. If **Oraldiscomfort** is NOT marked above, proceed to "Diet 3".	**Diet3:** Based solely on how the mouth feels, what does the subject feel (s)he could try to eat if (s)he did not have to swallow (mark only one) ☐Solids ☐Liquids ☐Nothing by Mouth

OM will be assessed using the NCI CTCAE version 4.0 [25] as follows:

Adverse Event	Grade				
	1	2	3	4	5
Oral Mucositis	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

OM will also be assessed using the World Health Organization (WHO) grading scale [26]:

WHO Oral Mucositis Grade	
Grade 0 (None)	None
Grade 1 (Mild)	Oral soreness/erythema
Grade 2 (Moderate)	Oral soreness/erythema, ulcers, can tolerate solid foods
Grade 3 (Severe)	Oral soreness/erythema, ulcers, liquid diet only
Grade 4 (Life-threatening)	Oral alimentation is not possible

Patient-reported OM outcomes will be assessed using the Oral Mucositis Daily Questionnaire (OMDQ) [27]

OralMucositisDailyQuestionnaire

2. During the PAST 24 HOURS how much MOUTH AND THROAT SORENESS DID YOU HAVE? *(Circle one number)*

0	1	2	3	4
No soreness	A little soreness	Moderate soreness	Quite a lot of soreness	Extreme soreness

3. During the PAST 24 HOURS how much did MOUTH AND THROAT SORENESS limit you in each of the following activities:

	Not limited	Limited a little	Limited some	Limited a lot	Unable to do
a. Swallowing	0	1	2	3	4

b. Drinking	0	1	2	3	4
c. Eating	0	1	2	3	4
d. Talking	0	1	2	3	4
e. Sleeping	0	1	2	3	4

4. On a scale of 0 to 10, how would you rate your OVERALL MOUTH AND THROAT SORENESS during the PAST 24 HOURS? *(Please circle the most appropriate number)*

0	1	2	3	4	5	6	7	8	9	10
None										Worst possible

*Questions 2 through 4 of OMDQ adapted from Elting et al, 2008 [27]

Dysphagia will be assessed using the NCI CTCAE version 4.0 [25] as follows:

Adverse Event	Grade				
	1	2	3	4	5
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death

Xerostomia will be assessed using the NCI CTCAE version 4.0 [25] as follows:

Adverse Event	Grade				
	1	2	3	4	5
Dry Mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva	-	-

Dysgeusia will be assessed using the NCI CTCAE version 4.0 [25] as follows:

Adverse Event	Grade				
	1	2	3	4	5
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-

Dermatitis will be assessed using the NCI CTCAE version 4.0 [25] as follows:

Adverse Event	Grade				
	1	2	3	4	5
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to	Moist desquamation in areas other than skin folds and	Life-threatening consequences; skin necrosis or ulceration of full	Death

		skin folds and creases; moderate edema	creases; bleeding induced by minor trauma or abrasion	thickness dermis; spontaneous bleeding from involved site; skin graft indicated	

Trismus
The interincisal distance will be measured in millimeters at the patient's maximum comfortable extent of mouth opening. Measurements will be taken at baseline, the last day of treatment, two-week follow-up, and 3 month follow-up appointments.

QualityofLife
QOL will be assessed at the time of enrollment prior to initiation of treatment, on the last day of treatment, and on the last day of study participation, 3 months after completion of radiation. This will be assessed using the Functional Assessment of Cancer Therapy: General (FACT-G) version 4 (Appendix 11.7).

QOL as related to head and neck cancer will be assessed at each follow-up appointment using the FACT – H&N version 4 (Appendix 11.8).

6.0 StatisticalConsiderations

6.1 PrimaryEndpoints:

- The incidence of severe (WHO grade 3-4) oral mucositis in patients treated to a cumulative radiation dose of at least 5000 cGy.
- The incidence of severe (CTCAE v. 4.0 grade 3-5) oral mucositis in patients treated to a cumulative radiation dose of at least 5000 cGy.

6.2 SecondaryEndpoints:

- Time to onset of severe (CTCAE v. 4.0 grade 3-4) oral mucositis following the initiation of radiotherapy.
- Mean cumulative radiation dose at time of onset of severe (CTCAE v. 4.0 grade 3-4) oral mucositis.
- Duration of oral mucositis.
- The incidence of pain.
- The incidence of dysphagia (CTCAE v. 4.0 and via diet assessment).
- The incidence of xerostomia (CTCAE v. 4.0).
- The incidence of dysgeusia (CTCAE v. 4.0).
- The incidence of trismus (Measurement of interincisal distance).
- The incidence of radiodermatitis (CTCAE v. 4.0).
- Evaluation of OM-related QOL (via FACT-H&N score).
- Incidence of any grade oral mucositis in patients treated to a cumulative radiation dose of at least 5000 cGy.

6.3 ExploratoryEndpoints:

- Proportion of patients with severe (CTCAE v. 4.0 grade 3-4) oral mucositis by 5000 and 7000 cGy.
- Proportion of patients with severe (CTCAE v. 4.0 grade 3-4) oral mucositis by schedule of chemotherapy given (weekly versus Q 3 weeks).
- Time to reach planned dose of radiation therapy.
- Amount of narcotic analgesia use during treatment.
- Assessments of breaks in treatment defined as one of the following:
    - Missing at least 1 chemotherapy treatment;
    - Dose reduction in planned cisplatin administration; OR
    - 3 consecutive days of no RT secondary to mucositis. ˜
- Proportion of patients who require feeding tube placement during treatment (excluding patients who received a prophylactic feeding tube prior to the initiation of therapy).
- Percent change in body weight during the course of treatment.

6.4 SampleSize

Previous studies (detailed in Section 2.2, Table 1) indicate that approximately 40% of patients will experience severe OM with radiation and concurrent chemotherapy. The hypothesis in this trial is that the addition of LLLT to this treatment regimen will decrease the rate of severe acute OM to 20%. A sample size of 45 yields 90% power to detect a difference of 0.20 using an exact one-sided binomial test with a Type I error of 0.05. A total of 50 patients are required to ensure that there are at least 45 compliant with the treatment schedule. Subjects who miss >20% of planned LLLT treatments will be considered non-compliant with the protocol. All patients should be enrolled in 12 months after the trial opens. We plan to enroll 25 patients at our institution. The same protocol will be opened separately at the University of Pittsburgh Medical Center (UPMC), where an additional 25 patients will be enrolled. A Data Use Agreement will allow combination of the data for a total of 50 patients to be analyzed.

6.5 Analysis

Primary endpoint

If 12 or fewer out of the 45 evaluable severe OM events occur (WHO grade 3-4 or CTCAE v. 4.0 grade 3-5 oral mucositis), we will reject the null hypothesis that the occurrence of severe OM is 0.4 with the addition of LLLT therapy. Point and 90% confidence intervals (using Wilson's method) will also be estimated to describe the primary endpoint.

Secondary endpoints

Descriptive statistics (point and exact 90% confidence interval estimates from the resultant Kaplan-Meier curve) will be generated for the time-to-severe OM and duration of severe OM endpoints. Point and 90% confidence intervals (using Wilson's method) will also be estimated to describe the binary endpoints. Continuous endpoints will be described by 90% confidence intervals using the t-distribution.

Exploratory endpoints
Similar descriptive analyses as described in the above paragraph will be used for the binary, time-to-event and continuous endpoints.

6.6 EvaluationofToxicity

All registered patients will be evaluated for toxicity probably related to the treatment. There have been no reported toxicities directly attributed to intraoral or extraoral LLLT. No systemic toxicities (e.g fever, nausea, fatigue) are anticipated or have been reported in association with oral LLLT. No specific toxicity is expected attributable to LLLT due to the addition of LLLT in patients receiving radiation with concurrent chemotherapy. Toxicity data will be collected at least weekly during the course of treatment to ensure the validity of this claim.

6.7 SpecificToxicOutcomes

No toxicities or dose-limiting toxicities have been reported in association with LLLT in the biomedical literature. Specifically with respect to LLLT for the prevention and/or management of oral mucositis, no toxicities or DLTs have been reported. Any toxicities arising would be anticipated to be localized to the exposed tissues. These would include undesignated skin/mucosal changes, such as localized skin erythema, mucosal swelling (not typically associated with mucositis) or unanticipated sensory changes. Of note, oral mucositis may develop despite LLLT and will not be considered a treatment-related toxicity.

We will closely monitor the following outcomes: grade 3 oral dysesthesia (burning/tingling sensation in the distribution exposed to LLLT), grade 3 or 4 oral mucosal swelling not attributable to mucositis (GI Disorders, other, specify), Grade 3 erythema and/or pain of the skin (in the distribution exposed to LLLT),visual loss, blurred vision, retinal tear or detachment, uveitis, or other eye disorders. If 2 or more patients out of the first 10 (or fewer) treated in the phase II portion of the study develop a grade III (using the CTCAE guidelines) or higher toxicity in any of these categories that are probably or definitely related to the LLLT treatment received within the first 2 weeks after the completion of treatment, we would recommend revisiting the study for safety reasons. Adjudication is necessary to ensure that we judge this study based on adverse events that are specific to LLLT therapy and not any other therapy that the patient happens to receive. We will continue to monitor these specific toxic outcomes throughout the course of the trial, in a sliding window fashion.

6.8 Othertoxicoutcomes

Data on other toxic side effects (excluding those detailed in the previous paragraph) that patients may experience will also be collected. We have chosen a safety threshold of 0.25 to monitor other toxic side effects. We would recommend termination of the phase II portion of the study for safety reasons if there were X many occurrences of grade 3 or higher toxicity (using the CTCAE guidelines) among the first N (or fewer) patients treated, as it would result in an upper confidence limit greater than 0.25:

N	X	p	UCL
8	1	0.125	0.255
13	2	0.154	0.256
18	3	0.167	0.253
22	4	0.181	0.261
27	5	0.185	0.256
32	6	0.188	0.252
36	7	0.194	0.256
41	8	0.185	0.252

In the above table, N = the number of patients treated; X = the cumulative number of patients with a grade 3 or higher toxicity currently observed; p = the observed toxicity rate; and UCL = the exact 1-sided upper 80% confidence limit for p, using Wilson's method without a continuity correction. After treating 41 patients, the potential toxicity risk of this regimen should be well defined, and thereafter the possible need for termination of the study based on toxicity should be minimal.

6.9 Expectedaccrualrate,accrua lduration,andstudyduration

Our anticipated accrual rate at our center is 25 patients per year. The accrual rate per year at UPMC will also be 25 patients per year. Thus, it should take approximately 1 year to accrue the maximum 50 patients needed for the data analysis. Allowing for 2 weeks of follow-up to obtain the primary endpoint on the last patient enrolled and 4 months to assemble, analyze and interpret the data the total study duration is projected to be at most 1.5 years.

7.0 AdverseEventsandSafetyMonitoring

There have been no reported toxicities directly attributed to oral LLLT for the prevention/ management of mucositis. Any toxicity would be expected to be localized to the region exposed (e.g. erythema of the skin, hyperalgesia). We do not anticipate treatment-related toxicity. LLLT has never been demonstrated to exacerbate or potentiate mucositis. Regardless, subjects will be followed carefully for any possible toxicity. Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. These will be followed per WSU IRB requirements.

7.1 ReportingofSeriousTreatmentEmergentAdverseEvents

An adverse event for the purposes of this protocol is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed consent even if the event is not considered to be related to the study intervention. Please refer to the adverse event section of the protocol for the protocol-specific definitions of study drug and study treatment.

The descriptions and grading scales found in the revised NCI CTCAE version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, or grades 1 - 4, will be used. Adverse event monitoring should be continued for at least 3 months following the last LLLT treatment.

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form will be recorded as part of the medical history or current medical condition. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy (e.g., any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events Case Report Form (CRF) under the signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded on the Adverse Events CRF. SAEs occurring after signing the Informed Consent are recorded on the Adverse Event CRF.

7.2 AdverseEventCharacteristics

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE grade 1-4)
2. Its relationship to each study treatment (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)
4. Action taken (no action taken/temporarily interrupted; study treatment permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. Whether it is serious, where a serious adverse event (SAE) is defined as one which:
   - Is fatal or life-threatening
   - Results in persistent or significant disability/incapacity
   - Constitutes a congenital anomaly/birth defect
   - Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
   - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)

- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Unlike routine safety assessments, SAEs a re monitored continuously and have special reportingrequirements;seeprotocolsect ionSeriousAdverseEventreporting.

All adverse events should be treated appropriately. Once an adverse event is detected, it should be followed until its resolution, an assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to the study treatment, any of the interventions required to treat it, and its outcome.

Information about all serious adverse events will be collected and recorded. A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Events **not** considered to be serious adverse events are hospitalizations for the routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.

- Sores in the mouth and throat that are likely to interfere with swallowing
- Temporary hair loss (of the face/chin/neck)
- Tanning, redness, or blistering or peeling of skin in treatment area
- Loss of teeth, or cavities in teeth, if strict dental care is not followed
- Hardness and tightness of the skin and muscles of the head and neck
- Dryness of the mouth or altered taste that may be permanent
- Loss of appetite

- Weight loss which may necessitate the placement of a temporary feeding tube
- Nausea and/or vomiting
- Weakness
- Hearing loss, ringing of the ears
- Numbness of the fingers and toes
- Lower blood counts with risk of infection or bleeding
- Anemia
- Loss of taste
- Muscle cramps
- Loss of coordination
- Involuntary movement
- Restlessness
- Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- Treatment on an emergency, outpatient basis for an event **not** fulfilling any of the definitions of serious given above and **not** resulting in hospital admission.

7.3 WSUIRBAdverseEventreporting

All adverse event reporting will be done in compliance with the Wayne State Institutional Review Board as follows:

A. Death or Life Threatening Adverse Reaction or Unexpected Event:
If a death or immediately life-threatening Adverse Reaction/Unexpected Event occurs, it must be reported to the IRB office within three (3) business days of the PI becoming aware, even if the information in the report is incomplete. As more information is forthcoming, one or more additional reports should be filed with the IRB. The initial report of the Adverse Reaction or Unexpected Event and follow-up reports should be filed using the IRB Adverse Reaction and Unexpected Event Form.

B. Serious Adverse Reaction or Unexpected Event:
If a Serious Adverse Reaction/Unexpected Event occurs (one that necessitates or prolongs hospitalization, results in a permanent or significant disability or congenital anomaly, or is judged to be serious by the principal investigator), and is **unexpected**, (not listed in the consent form) it must be reported to the IRB within five (5) business days of the PI becoming aware. If the Serious Adverse Event **is** listed in the consent form but a relationship to the study intervention/activity **cannotberuledoutbythePI**, it must be reported to the IRB within five (5) business days. If the information is incomplete on the initial filing, follow-up reporting is required. The IRB Adverse Reaction and Unexpected Event Form should be used in all reports pertaining to these reactions/events.

C. Non-Serious (Moderate or Minor) Adverse Reaction or Unexpected Event:
If a non-serious Adverse Reaction occurs that is **unexpected** (not listed in the informed consent), it must be reported to the IRB within ten (10) business days of awareness, **unlessthePrincipal Investigatorcanruleouttherelationshi ptothestudyagentorintervention.**If a non-serious Adverse Reaction occurs that is **expected** (listed in the informed consent), but is more frequent,

more intense or longer lasting that expected, or requires medical treatment, it must be reported to the IRB within ten (10) business days. If the reaction that is listed in the consent form occurs as described in the informed consent, **itdoesnotneedtobereportedtotheIRB.**
If an Unexpected Event occurs, it must be reported to the IRB within ten (10) business days of the awareness by the Principal Investigator. The Adverse Reaction/ Unexpected Event Form should be used for these submissions.

D. Possibly-Related Adverse Reactions/ Unexpected Events
In the rare case where a sponsor requires that a non-reportable (i.e., possibly related) Adverse Reaction/ Unexpected Event be reported to the IRB, an amendment should be submitted by the PI requesting that the non-reportable safety report be appended to the IRB file. It remains the primary responsibility of the WSU PI, the study sponsor, and any associated DSMB to identify trends that might require the event to be elevated to definitely or probably related status.
If a trend is identified that elevates the Adverse Reaction to definitely or probably related status, an Adverse Reaction/ Unexpected Event Form should be completed, along with an amendment for consent form changes, if needed, and submitted to the IRB.

7.4 Data Safety Monitoring

All charts to be reviewed and data recorded and analyzed using federal and institutional HIPAA guidelines. The data will be housed in a password-protected database that will be accessible only to the primary investigator.

Scheduled meetings will be held monthly or more frequently depending on the activity of the protocol. These meetings will include the protocol investigators and supporting staff involved with the conduct of the protocol.

During these meetings the investigators will discuss:

- Safety of protocol participants (adverse events and reporting)
- Validity and integrity of the data (data completeness on case report forms and complete source documentation)
- Enrollment rate relative to expectation of target accrual, (eligible and ineligible participants)
- Retention of participants, adherence to the protocol and protocol violations
- Protocol amendments

Completed Data and Safety Monitoring Reports of these regular investigator meetings will be kept on file in the office of the Clinical Trials Core (see form in appendix 11.10). The data manager assigned to the clinical trial will be responsible for completing the report form. The completed reports will be reviewed and signed off by the Principle Investigator (PI) or by one of the Co-PI's in the absence of the PI. The signed off forms will then be forwarded to the Director, Clinical Trials Core for review of completeness and processing with the Data and Safety Monitoring Committee.

The Barbara Ann Karmanos Cancer Institute, Data and Safety Monitoring Committee will meet on a monthly basis to review the prior month Serious Adverse Event forms and Data and Safety Monitoring study specific reports that have been filed.

7.5 Ethics

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements.

The final study protocol, including the final version of the Written Informed Consent Form, must be approved in writing by Wayne State University IRB or the IRB of the respective institution.

The principal investigator is responsible for informing the Wayne State University IRB of any amendments to the protocol. The protocol must be re-approved by the IRB annually. Progress reports and notifications of serious, unexpected adverse events or drug reactions will be provided to the IRB.

The principal investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. In accordance with the Health Information Portability and Accountability Act (HIPAA), the Written Informed Consent Form must include a subject authorization to release medical information to any agency, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

The principal investigator must store the original, signed Written Informed Consent Form. A copy of the signed Written Informed Consent Form must be given to the subject.

8.0 RegistrationProcedures

8.1 GeneralGuidelines

Eligible patients will be entered on the study centrally at the clinical trials office of the Karmanos Cancer Center/Wayne State University, by the Study Coordinator.

At the time of registration:

- Patients must have signed an informed consent form prior to registration.
- Confirm that all required pre-study requirements are completed as per the study calendar.
- Collect demographic information on the patient including age, gender, smoking history, alcohol history, tumor stage, histology, prior therapy.

8.2 RegistrationProcess

To register a patient, the following documents should be completed and faxed or e-mailed to the Study Coordinator:

- Signed patient consent form
- HIPAA authorization form

9.0 ProtocolConductandGuidelines

9.1 Protocolamendments,orchangesinstudyconduct

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed and approved. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB.

If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes.

9.2 Publicationofresults

Data from the results of this study will be combined with the data from the results of the same protocol submitted at the University of Pittsburgh Medical Center and will be published together in one collective report. The results of this study will be presented in abstract form in an international medical conference forum and published in a peer-reviewed journal.

9.3 EthicsandGoodClinicalPractice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in:

- ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
- US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
- Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

9.4 InstitutionalReviewBoard/IndependentEthicsCommittee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB).

9.5 Informedconsent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time

and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

9.6 DeclarationofHelsinki

The investigator will conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

10.0References

1. Pfister, D.G., et al., *Head and Neck Cancers, Version 1.2015.* J Natl Compr Canc Netw, 2015. **13**(7): p. 847-56.
2. Trotti, A., et al., *Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review.* Radiother Oncol, 2003. **66**(3): p. 253-62.
3. Cheng, K.K., et al., *Severe oral mucositis associated with cancer therapy: impact on oral functional status and quality of life.* Support Care Cancer, 2010. **18**(11): p. 1477-85.
4. Groome, P.A., et al., *Compromised local control due to treatment interruptions and late treatment breaks in early glottic cancer: Population-based outcomes study supporting need for intensified treatment schedules.* Int J Radiat Oncol Biol Phys, 2006. **64**(4): p. 1002-12.
5. Elting, L.S., et al., *Risk, outcomes, and costs of radiation-induced oral mucositis among patients with head-and-neck malignancies.* Int J Radiat Oncol Biol Phys, 2007. **68**(4): p. 1110-20.
6. Huang, Y.Y., et al., *Biphasic dose response in low level light therapy - an update.* Dose Response, 2011. **9**(4): p. 602-18.
7. Kim, W.S. and R.G. Calderhead, *Is light-emitting diode phototherapy (LED-LLLT) really effective?* Laser Ther, 2011. **20**(3): p. 205-15.
8. Sutherland, J.C., *Biological effects of polychromatic light.* Photochem Photobiol, 2002. **76**(2): p. 164-70.
9. Karu, T., *Laser biostimulation: a photobiological phenomenon.* J Photochem Photobiol B, 1989. **3**(4): p. 638-40.
10. Karu, T.I. and S.F. Kolyakov, *Exact action spectra for cellular responses relevant to phototherapy.* Photomed Laser Surg, 2005. **23**(4): p. 355-61.
11. Antunes, H.S., et al., *Phase III trial of low-level laser therapy to prevent oral mucositis in head and neck cancer patients treated with concurrent chemoradiation.* Radiother Oncol, 2013. **109**(2): p. 297-302.
12. Arun Maiya, G., M.S. Sagar, and D. Fernandes, *Effect of low level helium-neon (He-Ne) laser therapy in the prevention & treatment of radiation induced mucositis in head & neck cancer patients.* Indian J Med Res, 2006. **124**(4): p. 399-402.
13. Arora, H., et al., *Efficacy of He-Ne Laser in the prevention and treatment of radiotherapy-induced oral mucositis in oral cancer patients.* Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2008. **105**(2): p. 180-6, 186 e1.
14. Bensadoun, R.J., et al., *Low-energy He/Ne laser in the prevention of radiation-induced mucositis. A multicenter phase III randomized study in patients with head and neck cancer.* Support Care Cancer, 1999. **7**(4): p. 244-52.
15. Gautam, A.P., et al., *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, 2015. **144**: p. 51-6.
16. Gautam, A.P., et al., *Low level laser therapy for concurrent chemoradiotherapy induced oral mucositis in head and neck cancer patients - a triple blinded randomized controlled trial.* Radiother Oncol, 2012. **104**(3): p. 349-54.
17. Lima, A.G., et al., *Efficacy of low-level laser therapy and aluminum hydroxide in patients with chemotherapy and radiotherapy-induced oral mucositis.* Braz Dent J, 2010. **21**(3): p. 186-92.

18. Zanin, T., et al., *Use of 660-nm diode laser in the prevention and treatment of human oral mucositis induced by radiotherapy and chemotherapy.* Photomed Laser Surg, 2010. **28**(2): p. 233-7.
19. Carvalho, P.A., et al., *Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: a double-blind randomized study in head and neck cancer patients.* Oral Oncol, 2011. **47**(12): p. 1176-81.
20. Oton-Leite, A.F., et al., *Effect of intraoral low-level laser therapy on quality of life of patients with head and neck cancer undergoing radiotherapy.* Head Neck, 2012. **34**(3): p. 398-404.
21. Bjordal, J.M., et al., *A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis.* Support Care Cancer, 2011. **19**(8): p. 1069-77.
22. Lalla, R.V., et al., *MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy.* Cancer, 2014. **120**(10): p. 1453-61.
23. Peterson, D.E., et al., *Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines.* Ann Oncol, 2011. **22 Suppl 6**: p. vi78-84.
24. Brouwer, C.L., et al., *CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines.* Radiother Oncol, 2015. **117**(1): p. 83-90.
25. Institute, N.C., *Common Terminology Criteria for Adverse Events v4.0* in *NIH publication # 09-7473*, N. NCI, DHHS. , Editor.
26. Organization, W.H., *WHO handbook for reporting results of cancer treatment*. 1979: Geneva : World Health Organization.
27. Elting, L.S., et al., *Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life.* Cancer, 2008. **113**(10): p. 2704-13.

11.0 Appendix

11.1 Karnofsky Performance Scale
11.2 Weekly Toxicity Scoring Sheet
11.3 LLLT Treatment Record Form
11.4 Table 2. Consensus Contouring Guidelines for Organs at Risk
11.5 Table 3. OAR dose parameters to be recorded
11.6 FACT-G
11.7 FACT-H&N
11.8 Oral Mucositis Daily Questionnaire (OMDQ)
11.9 Data and Safety Monitoring Report
11.10 Study Calendar

11.1 KarnofskyPerformanceScale

KARNOFSKYPERFORMANCESCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

11.2 WeeklyToxicityScoringSheet

Protocol ID_____ Subject number_____ Assessment date_____ Radiation dose_____

Assessment type: ☐Baseline ☐Weekly ☐Last Treatment ☐Follow-up

Mouth Pain (0-10) _____ Throat Pain (0-10) _____ PEG tube (Y / N) Alcohol use (Y / N) Smoking (Y / N) Weight_____kg

Analgesics (medications and dose)_____

DietAssessment		
Diet1: What has the subject been able to eat within the past 24 hours (mark only one) ☐Solids ☐Liquids ☐Nothing by Mouth If **Solids** is marked above, proceed to next section. If **Liquids** or **NothingbyMouth** is marked about continue to "Diet 2".	**Diet2:** If the subject has been unable to eat Solid food, mark all the reason(s) why (mark all that apply) ☐Nausea/Vomiting ☐Oral discomfort ☐Loss of appetite ☐Dry mouth ☐Throat discomfort ☐No teeth ☐Difficulty Swallowing ☐Other_____ If **Oraldiscomfort** is marked above, proceed to the next section. If **Oraldiscomfort** is NOT marked above, proceed to "Diet 3".	**Diet3:** Based solely on how the mouth feels, what does the subject feel (s)he could try to eat if (s)he did not have to swallow (mark only one) ☐Solids ☐Liquids ☐Nothing by Mouth

WHO Oral Mucositis Grade	
Grade 0 (None)	None
Grade 1 (Mild)	Oral soreness/erythema
Grade 2 (Moderate)	Oral soreness/erythema, ulcers, can tolerate solid foods
Grade 3 (Severe)	Oral soreness/erythema, ulcers, liquid diet only
Grade 4 (Life-threatening)	Oral alimentation is not possible

Adverse Event	Grade				
	1	2	3	4	5
Oral Mucositis	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

Adverse Event	Grade				
	1	2	3	4	5
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death

Adverse Event	Grade				
	1	2	3	4	5
Dry Mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva	-	-

Adverse Event	Grade				
	1	2	3	4	5
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-

Adverse Event	Grade				
	1	2	3	4	5
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death

Signature_____

11.3 LLLTTreatmentRecordForm

Subject ID:_____

Radiationstartdate_____		Monday(Date_____)			Wednesday(Date_____)			Friday(Date_____)			Notes:
		Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	
Week1	Right buccal mucosa*										
	Left buccal mucosa*										
	Ventral tongue*										
	Upper lip										
	Lower lip										
	Right tongue										
	Left tongue										
	Hard Palate										
	Soft palate										
	Floor of mouth										
	Other sites:										

		Monday(Date_____)			Wednesday(Date_____)			Friday(Date_____)			Notes:
		Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	
Week2	Right buccal mucosa*										
	Left buccal mucosa*										
	Ventral tongue*										
	Upper lip										
	Lower lip										
	Right tongue										
	Left tongue										
	Hard Palate										
	Soft palate										
	Floor of mouth										
	Other sites:										

*Required treatment area (other areas treated if symptomatic)
†1 minute / 2.5Hz

Signature_____

11.3 LLLT Treatment Record Form

Subject ID:_____

		Monday(Date_____)			Wednesday(Date_____)			Friday(Date_____)			Notes:
		Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	
Week3	Right buccal mucosa*										
	Left buccal mucosa*										
	Ventral tongue*										
	Upper lip										
	Lower lip										
	Right tongue										
	Left tongue										
	Hard Palate										
	Soft palate										
	Floor of mouth										
	Other sites:										

		Monday(Date_____)			Wednesday(Date_____)			Friday(Date_____)			Notes:
		Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	
Week4	Right buccal mucosa*										
	Left buccal mucosa*										
	Ventral tongue*										
	Upper lip										
	Lower lip										
	Right tongue										
	Left tongue										
	Hard Palate										
	Soft palate										
	Floor of mouth										
	Other sites:										

*Required treatment area (other areas treated if symptomatic)
†1 minute / 2.5Hz

Signature_____

11.3 LLLT Treatment Record Form

Subject ID:_____

		Monday(Date_____)			Wednesday(Date_____)			Friday(Date_____)			Notes:
		Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	
Week5	Right buccal mucosa*										
	Left buccal mucosa*										
	Ventral tongue*										
	Upper lip										
	Lower lip										
	Right tongue										
	Left tongue										
	Hard Palate										
	Soft palate										
	Floor of mouth										
	Other sites:										

		Monday(Date_____)			Wednesday(Date_____)			Friday(Date_____)			Notes:
		Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	
Week6	Right buccal mucosa*										
	Left buccal mucosa*										
	Ventral tongue*										
	Upper lip										
	Lower lip										
	Right tongue										
	Left tongue										
	Hard Palate										
	Soft palate										
	Floor of mouth										
	Other sites:										

*Required treatment area (other areas treated if symptomatic)
†1 minute / 2.5Hz

Signature_____

11.3 LLLT Treatment Record Form

Subject ID:_____

		Monday(Date_____)			Wednesday(Date_____)			Friday(Date_____)			Notes:
		Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	
Week7	Right buccal mucosa*										
	Left buccal mucosa*										
	Ventral tongue*										
	Upper lip										
	Lower lip										
	Right tongue										
	Left tongue										
	Hard Palate										
	Soft palate										
	Floor of mouth										
	Other sites:										

		Monday(Date_____)			Wednesday(Date_____)			Friday(Date_____)			Notes:
		Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	
Week8	Right buccal mucosa*										
	Left buccal mucosa*										
	Ventral tongue*										
	Upper lip										
	Lower lip										
	Right tongue										
	Left tongue										
	Hard Palate										
	Soft palate										
	Floor of mouth										
	Other sites:										

*Required treatment area (other areas treated if symptomatic)
†1 minute / 2.5Hz

Signature_____

11.3 LLLT Treatment Record Form

Subject ID:_____

		Monday(Date_____)			Wednesday(Date_____)			Friday(Date_____)			Notes:
		Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	
Week9	Right buccal mucosa*										
	Left buccal mucosa*										
	Ventral tongue*										
	Upper lip										
	Lower lip										
	Right tongue										
	Left tongue										
	Hard Palate										
	Soft palate										
	Floor of mouth										
	Other sites:										

		Monday(Date_____)			Wednesday(Date_____)			Friday(Date_____)			Notes:
		Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	Mucositis (Y/N)	Treated Area (Y/N)	Treated Area Settings†: (Y/N)	
Week10	Right buccal mucosa*										
	Left buccal mucosa*										
	Ventral tongue*										
	Upper lip										
	Lower lip										
	Right tongue										
	Left tongue										
	Hard Palate										
	Soft palate										
	Floor of mouth										
	Other sites:										

*Required treatment area (other areas treated if symptomatic)
†1 minute / 2.5Hz

Signature_____

11.4 Table2.ConsensusContouring GuidelinesforOrgansatRisk

OrganatRisk	Remarks	AnatomicBoundaries					
		Cranial	Caudal	Anterior	Posterior	Lateral	Medial
Required							
Parotid gland	Include carotid artery, retromandibular vein and extracranial facial nerve.	External auditory canal, mastoid process	Post. part submandibular space	Masseter m., post. border mandibular bone, med. and lat. pterygoid m.	Ant. belly sternocleidomastoid m., lat. side post. belly of the digastric m. (posterior- medial)	Subcutaneous fat, platysma	Post. belly of the digastric m., styloid process, parapharyngeal space
Submandibular gland		Med. pterygoid m., mylohyoid m.	Fatty tissue	Lat. Surface mylohyoid m., hyoglossus m.	Parapharyngeal space, sternocleidomastoid m.	Med. surface med. pterygoid m., med. surface mandibular bone, platysma	Lat. surface mylohyoid m., hyoglossus m., superior and middle pharyngeal constrictor m., anterior belly of the digastric m.
Extended oral cavity	Posterior to mandible and maxilla, no inner surface of the lips	Hard palate mucosa and mucosal reflections near the maxilla	The base of tongue mucosa and hyoid posteriorly and the mylohyoid m. and ant. belly of the digastric m. anteriorly	Inner surface of the mandible and maxilla	Post. borders of soft palate, uvula, and more inferiorly the base of tongue	Inner surface of the mandible and maxilla	
Lips		Hard palate (lateral), anterior nasal spine (at the midline)	Lower edge teeth sockets, cranial edge mandibular body	Outer surface of the skin	Mandibular body, teeth, tongue, air (if present)	Depressor anguli oris m., buccinator m., levator anguli oris m./risorius m. Buccinator	
Buccal mucosa		Bottom of maxillary sinus	Upper edge teeth sockets	Lips, teeth	Med. pterygoid m.	Buccal fat	Outer surface of the mandible and maxilla, oral cavity/base of tongue/soft pallate
Pharyngeal constrictor muscle	Thickness ~3 mm	Caudal tips of pterygoid plates	Caudal edge of arytenoid cartilages	Superior: hamulus of pterygoid plate; mandibula; base of tongue; pharyngeal lumen. Middle: base of tongue; hyoid. Inferior: soft tissue of	Prevertebral muscle	Superior: medial pterygoid muscle. Middle: greater horn of hyoid bone. Inferior: superior horn of thyroid	

				supraglottic/glottic larynx		cartilage	
Optional							
Supraglottic larynx		Tip of epiglottis	Cranial edge of arytenoid cartilages	Hyoid bone, pre-epiglottic space, thyroid cartilage	Inferior PCM, pharyngeal lumen	Thyroid cartilage	Pharyngeal lumen (lumen excluded)
Glottic area		Cranial edge of arytenoid cartilages	Caudal edge of ant. part of thyroid cartilage		Cricoid, anterior border arytenoids		
Crico-pharyngeal inlet		Caudal edge of arytenoid cartilages	1 cm caudal to the lower edge of the cricoid cartilage	Tracheal lumen	Vertebral body		
Cervical esophagus		1 cm caudal to the lower edge of the cricoid cartilage	Caudal edge of C7				
Brachial plexus	If the brachial plexus is wrapped around the vascular bundle on the most inferior slices, the vascular structure is included in the contour	Cranial border of C5, vertebral body	Cranial border of T3, vertebral body	Post. border of: anterior scalene m., subclavian artery, axillary vein	Ant. border of: middle scalene m., seratus anterior m., subscapularis m.	Lat. border of: ant. and middle scalene m., pectoralis major, teres major	Intervertebral foramen (bony vertebral body), lat. border of 1st rib

Organs at risk with specification of anatomic boundaries. Ant. = anterior, post. = posterior, lat. = lateral, med. = medial, m. = muscle.

Table adapted from:
Brouwer CL et al. CT-based delineation of organs at risk in the head and neck region: DAHANCA, EORTC, GORTEC, HKNPCSG, NCIC CTG, NCRI, NRG Oncology and TROG consensus guidelines. Radiother Oncol (2015). [24]

11.5 Table3.OARdosepa rameterstoberecorded

Brainstem	Maximum Dose_____	
SpinalCord	Maximum Dose_____	
RightParotid	Mean Dose_____	$V30_{Gy}$_____
LeftParotid	Mean Dose_____	$V30_{Gy}$_____
Parotids(bilateral)	D20cc_____	
SubmandibularGland	Mean Dose_____	
ExtendedOralCavity	Maximum Dose_____	Mean Dose_____
Lips	Maximum Dose_____	Mean Dose_____
BuccalMucosa	Maximum Dose_____	Mean Dose_____
Mandible	Maximum Dose_____	
PharyngealConstrictors	Mean Dose_____	

11.6 FACT-G(Version4)

Below is a list of statements that other people with your illness have said are important.**Pleasecircle ormarkonenumberperlineto indicateyourresponseasit appliestothepast7days.**

	PHYSICALWELL-BEING	**Not atall**	**Alittle bit**	**Some-what**	**Quite abit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILYWELL-BEING	**Not atall**	**Alittle bit**	**Some-what**	**Quite abit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-G(Version4)

Pleasecircleormarkonenumberperlinetoindica teyourresponseasitappliestothepast7____ days.

	EMOTIONALWELL-BEING	Not atall	Alittle bit	Some-what	Quite abit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONALWELL-BEING	Not atall	Alittle bit	Some-what	Quite abit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

11.7 FACT-H&N(Version4)

Pleasecircleormarkonenumberperlinetoindica teyourresponseasitappliestothepast7_____ days.

	ADDITIONALCONCERNS	Notat all	Alittle bit	Some-what	Quite abit	Very much
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look.....	0	1	2	3	4
H&N7	I can swallow naturally and easily	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.).....	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods.....	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

11.8 OralMucositisDailyQuestionnaire

2. During the PAST 24 HOURS how much MOUTH AND THROAT SORENESS DID YOU HAVE? *(Circle one number)*

0	1	2	3	4
No soreness	A little soreness	Moderate soreness	Quite a lot of soreness	Extreme soreness

3. During the PAST 24 HOURS how much did MOUTH AND THROAT SORENESS limit you in each of the following activities:

	Not limited	Limited a little	Limited some	Limited a lot	Unable to do
a. Swallowing	0	1	2	3	4
b. Drinking	0	1	2	3	4
c. Eating	0	1	2	3	4
d. Talking	0	1	2	3	4
e. Sleeping	0	1	2	3	4

4. On a scale of 0 to 10, how would you rate your OVERALL MOUTH AND THROAT SORENESS during the PAST 24 HOURS? *(Please circle the most appropriate number)*

0	1	2	3	4	5	6	7	8	9	10
None										Worst possible

*Questions 2 through 4 of OMDQ adapted from Elting et al, 2008 [27]

11.9 Data and Safety Monitoring Report

Barbara Ann KARMANOS Cancer Institute: Protocol Specific Data and Safety Monitoring Report

PROTOCOL #: _____ **REPORT DATE:** _____

PROTOCOL TITLE		
ATTENDANCE		
PROTOCOL ACTIVITY SINCE LAST REPORT		
Accrual Goal:	Eligible:	Total number of AE's to date:
Accrual to Date:	Ineligible (provide reason):	
Accrual Since Last Monthly Report:		
Specifically for Phase I Trial &/or Dose Escalating Trials:		
Dose Level	**Accrual**	
1		
2		
3		

Record all Grade 3, 4, and 5 Adverse Events (AE). Group by category of AE. record the date OF the occurrence, attribution and if reportable to the IRB. Shade the rows of the AE's that have occurred for this Report. attach the HIC UP report form for these reportable events that occurred on this report.

Pt. ID#	Category and type of adverse reaction	Date of Occurrence	Grade[1]	Attribution[2]	Reportable to IRB (Y/N) Yes with date

1. Grade: 1-Mild, 2-Moderate, 3- Severe, 4-Life-threatening, or 5- Death.
2. Attribution: 1-unrelated, 2 - unlikely, 3 - possibly, 4 - probably, or 5 - definitely

OFF TREATMENT ˜ Provide reason [progression, death, toxicity, completed therapy, etc].
PROTOCOL VIOLATIONS Deviations from protocol treatment, monitoring, or study calendar.
PROTOCOL AMENDMENTS Include date submitted to regulatory bodies and date approved.

OTHERCOMMENTS			
InvestigatorSignature:		**DataManager Signature:**	

11.10 StudyCalendar

	Treatment (low-level laser therapy)					Follow Up (low-level laser therapy)	
	Pre-Study		Treatment Period		Last Day of Treatment	Follow Up Period	
	Screening -28 to -1	Baseline Day 0	Weekly Visit	Visits 3x/week	Last Day of Treatment	Follow Up Week 2	Follow Up Month 3
Medical History	X						
Demographics	X						
Physical Exam	X						
Assessment of Oral Mucositis (WHO)		X	X		X	X	X
Chemotherapy [1; AN]					X		
Organs at Risk Review (OAR) [2; AN]					X		
Radiation Therapy [3; AN]					X		
Dietary Assessment		X	X		X	X	X
Mouth Pain, Throat Pain, PEG Tube, Alcohol use, Smoking, Weight		X	X		X	X	X
FACT-G		X	X		X	X	X
Oral Mucositis Daily Questionnaire		X	X		X	X	X
FACT-H&N		X	X		X	X	X
Low-level Laser Therapy (LLLT) Treatment Record Form			X	X			
Trismus Assessment		X			X	X	X
Adverse Events: CTCAE (oral mucositis, dysphagia, xerostomia, dysgeusia, and dermatitis)		X	X		X	X	X
Concomitant Medications (for analgesia & mucositis)		X	X		X	X	X

Calendar Foot Notes

1. The prescribed course of chemotherapy will be determined by the managing medical oncologist per institutional practices and will not be altered based on this study.

2. Dose limits to OARs will be determined by institutional practice and specific dose-constraints will not be required on this protocol.

3. Radiation therapy will be delivered with an intensity modulated radiation therapy (IMRT) technique and/or image-guided radiation therapy (IGRT). The prescribed course of radiotherapy will not be altered based on this study. Radiotherapy will be delivered 5 days per week, Monday - Friday with one radiation treatment given per day. The planned cumulative dose of radiation will be determined by the treating physician and will range from 5000 - 7000 cGy in 180 - 200 cGy daily fractions over the course of 5-7 weeks. This treatment is not part of the research protocol.

AN. As Needed