CHAPTER II

REVIEW OF LITERATURE

An insight of Head and Neck Cancer, Oral Mucositis, Low level laser and evidence of Low level laser therapy for oral mucositis in details is given in this chapter.
CHAPTER II A

HEAD AND NECK CANCER

AN OVERVIEW

An insight of common carcinomas of the head and neck region and available treatment options is necessary before reciting particulars of the present research work. Therefore, this chapter endow with details of anatomy, common sites of carcinoma and current treatment methods of head and neck cancer.
2A.1 HEAD and NECK REGION

2A.1a Anatomy of Head and Neck Region

2A.1b The Oral Cavity

Various landmarks of the oral cavity includes: vestibule, vestibule fornix, labial mucosa, buccal mucosa, parotid papilla, Stensen’s duct, linea alba, Fordyce’s spots, alveolar mucosa, gingiva, labial frenum, and buccal frenum. Inside the mouth, a pocket is formed by the soft tissue of the cheeks and the gingiva called oral vestibule (muco-buccal fold). The deepest point of the vestibule is called the vestibule fornix, which forms a U-shaped pocket that is continuous throughout the anterior and posterior areas. The tissue that lines the inner surface of the lips and cheeks is called mucosa and is named according to its location. The inner surface of the lips is called the labial mucosa, and the inner surface of the cheeks is the buccal mucosa. On the labial mucosa are small, yellowish glands near the commissures called Fordyce’s spots, which become larger and more visible with age. On the buccal mucosa, opposite the maxillary second molar, is a flap of tissue called the parotid papilla, where lies the opening of the Stensen’s duct. On the buccal mucosa is a raised white line that runs parallel to where the teeth meet, called the linea
Mucosa also covers the alveolar bone that supports the teeth. It is called the alveolar mucosa. The alveolar mucosa is loosely attached and is highly vascular, giving the mucosa a reddish color. Moving from the alveolar mucosa toward the teeth is the gingiva. The gingiva is firmly attached and usually pale pink or brownish pink, depending on pigmentation. This dense, fibrous tissue covered with mucous membrane can withstand pressure during chewing. The portion of the gingiva that meets the tooth is called the free gingiva or marginal gingiva.

When the lips are pulled out, frena become visible. Frena (plural form of frenum) are raised lines of mucosal tissue that extend from the alveolar mucosa through the vestibule to the labial and buccal mucosa. On the labial, the main frena are between the maxillary central incisors and the mandibular central incisors, with minor frena along the vestibule of both arches in the labial and buccal areas.

**Palate Area of the Oral Cavity**

On the inside of the maxillary teeth is the palate, or “roof of the mouth.” The palate is divided into hard and soft palate. The hard palate, the anterior portion, is a bony plate covered with pink to brownish pink keratinized tissue. The soft palate, the posterior portion, covers muscle tissue and is darker pink or yellowish. On the hard palate is the incisive papilla, which is a raised area of tissue lying behind the maxillary central incisors. Extending from the back of the incisive papilla is a slightly raised line that extends down the middle of the hard palate, known as the palatine raphe. The ridges that run horizontally across the hard palate behind the incisive papilla are the palatine rugae. Occasionally, in the middle of the palate a lump or prominence of bone (exostosis) may be found. This excess bone is called a torus (plural is tori), or a torus palatinus, specifically. The following landmarks are on the soft palate and in the oropharynx areas: the uvula, anterior tonsillar pillars, posterior tonsillar pillars, palatine tonsils, and the fauces. The
uvula is a projection that extends off the back of the soft palate. Extending horizontally from the uvula to the base of the tongue are folds of tissue called anterior tonsillar pillars or palate-glossal arches. Another set of arches is found farther back in the throat. This set is the posterior tonsillar pillars or palate-pharyngeal arches. Between the two sets of pillars is a depressed area where the palatine tonsils are situated. The palatine tonsils are often marked with deep grooves and are red and inflamed due to infection. The space in the back of the oral cavity where food passes into the pharynx is the fauces.

**Tongue**

The tongue is a significant region of the oral cavity with the following landmarks: sulcus terminalis, circumvallate papilla, filiform papillae, fungiform papillae, foliate papilla, and median sulcus on the dorsal or top surface of the tongue. On the ventral or underside of the tongue are the lingual frenum, the lingual veins, and the fimbriated folds. When the tongue is extended, a shallow, V-shaped groove is apparent on the posterior portion called the sulcus terminalis. This groove separates the anterior two-thirds, or body of the tongue, from the base of the tongue. Anterior to the sulcus, covering the dorsal side of the tongue, are small, raised projections called papilla, where taste buds are located. The largest papilla, mushroom shaped, is anterior to the sulcus terminalis in a row of eight to ten and is called circumvallate papillae. Anterior to the circumvallate papillae and covering the dorsal side of the tongue are hair-like projections called filiform papillae. Papillae that give the tongue the “strawberry effect” are the fungiform papillae. On the lateral border of the tongue near the base are the foliate papillae, which are slightly raised, vertical folds of tissue. The tongue is divided in half by the median sulcus, which runs from the base to the tip of the tongue. Lateral to the lingual veins are folds of tissue called fimbriated folds.
Floor of the Mouth

The floor of the mouth includes the sublingual caruncles, sublingual folds, and sublingual sulcus. Where the lingual frenum attaches to the floor of the mouth are two small, raised folds of tissue, one on either side of the frenum. These are sublingual caruncles. On top of these folds of tissue lie the ducts of two salivary glands. The sublingual folds begin at the caruncles on either side of the frenum and run backward to the base of the tongue. Lateral to the sublingual fold is a horseshoe-shaped groove that follows the curve of the dental arch, called the sublingual sulcus. This sulcus marks the end of the alveolar ridge and the beginning of the floor of the mouth.

Salivary Glands

Three major pairs of salivary glands supply the oral cavity: parotid, submandibular, and sublingual. These glands secrete saliva to assist in the process of digestion. The largest of the salivary glands are the parotid glands, which lie just below and in front of the ear. The parotid glands empty into the mouth through the parotid duct (also known as Stensen’s duct). The duct empties into the mouth through the parotid papilla, which is just opposite the maxillary second molar. The submandibular glands are about the size of a walnut and lie on the inside of the mandible in the posterior area. They empty saliva into the mouth through the Wharton’s duct, which ends in the sublingual caruncles. The third set of glands and smallest are the sublingual glands, located on the floor of the mouth. These glands either empty directly into the mouth through the ducts of Rivinus or through the sublingual caruncles by means of the ducts of Bartholin. The ducts of the sublingual glands are similar in function to a “soaker hose.” There are also smaller minor salivary glands that are in the buccal, labial and lingual mucosa, the floor of the mouth, the posterior portion of the dorsal surface of the tongue, the soft palate, and the lateral (side) portions of the hard palate. The saliva from these glands is mucus saliva.42
2A.2 CARCINOMA OF HEAD AND NECK

2A.2a Definition:
Head and neck cancer is a general term applied for a group of biologically similar cancers that arise in the upper aero-digestive tract, including the lip, oral cavity (mouth), nasal cavity (inside the nose), paranasal sinuses, pharynx, and larynx. 90% of HNC are squamous cell carcinomas (SCC), originating from the mucosal lining (epithelium) of these regions. HNC often spread to the lymph nodes of the neck, and this is often the first (and sometimes only) sign of the disease at the time of diagnosis.

2A.2b Epidemiology:
Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. Globally about 12.7 million cancer cases and 7.6 million cancer deaths are estimated to have occurred in 2008; of these, 56% of the cancer cases and 64% of the cancer deaths occurred in the economically developing world. Cancer is a becoming a major health problem in India, with approximately 1 million cases occurring each year. Head and neck cancer is among the commonest cancers diagnosed in Indian Subcontinent.

Figure B

*Figure B: Incidence of Various cancers in Males and Females in India*
Over 200,000 cases of HNC occur each year in India verses 30,000 for the US. Cancer accounts for 8% of the deaths in India. The increasing number of HNC cases is a cause of major concern as it is associated with high morbidity and mortality. Over one third of all cancers in India, occurs in the head and neck compared to less than 10% in the Western world and 4% in the USA. The primary reason for this unusually high incidence of HNC in India is the indiscriminate use of chewing tobacco in its various forms. In tobacco users, the oral cavity bears the brunt of the carcinogen and nearly 80,000-100,000 oral cancers are diagnosed every year in the country.

HNC includes many different malignancies and the prevalence of HNC with respect to total body malignancies ranges from 9.8% to 42.7%. The most common site of HNC is oropharynx (28.6%) followed by esophagus (19.4%) and oral cavity (16.3%). Cancer of ear is least common (0.4%). In oral cavity most common cancer site is the tongue (32.7%) while buccal mucosa and tonsils accounted for more than 20%. (Figure C) Gender wise males develop HNC more frequently, than females with the ratio of almost 3:1. Oropharyngeal cancer is common in males while esophageal cancer is more common in females.

**Figure C:** Incidence of region vise distribution of Head and Neck cancers in India
Globally, the highest oral cavity cancer rates are found in Melanesia, Southern and Central Asia, and Central and Eastern Europe and the lowest in Africa, Central America, and Eastern Asia for both males and females). The incidence of HNC has been reported from 22-34% due to habits of chewing areca nut, smoking and alcohol use in coastal regions of South India. In Kasturba Hospital, Manipal (where present clinical trial was conducted), which is a tertiary care hospital based in South India, Cancer Registry Record from 1975-2011 revealed that on an average, registers 200 to 250 new HNC cases every year. This accounts to approximately 25% of all the newly diagnosed cancers presenting at our center annually. About 90% of the patients with head and neck cancers present in a locally advanced stage (Stage III & Stage IV) whereas only 10% present in an early stage. Even though patients with advanced stages of the disease have a poorer prognosis compared to early disease, a substantial number of patients are cured of their disease.

2A.2c Types of Head and Neck Cancer

Region wise

Head and Neck cancers are broadly classified based on their anatomical site of origin into cancers of oral cavity, oropharynx and larynx. Figure D

![Figure D](image)

**Figure D**: Regional distribution of Head and Neck cancers
2A.2d Histopathological Patterns

The most common histological type in HNC cases are Squamous cell carcinoma (SCC) (93.3%), followed by verrucous carcinoma (1.5%). Laryngeal and hypo-pharyngeal are almost exclusively SCC (100% and 99%, respectively). In cancers of the oral cavity, verrucous carcinoma comprised approximately 1.5% of the cases with the remainder SCC.47-49

2A.2e Risk Factors for HNC

Major risk factors for oral cavity cancer are Smoking, alcohol use, smokeless tobacco products, and HPV infections while smoking and alcohol having synergistic effects.50-56 The contribution of each of these risk factors to the burden varies across regions. Worldwide, smoking accounts for 42% of deaths from cancers of the oral cavity (including the pharynx) and heavy alcohol consumption for 16% of the deaths; the corresponding percentages in high-income countries are about 70% and 30%, respectively.50,51 Smokeless tobacco products and betel quid with or without tobacco are the major risk factors for oral cavity cancer in Indian Subcontinent.52-53

Oral cavity cancer mortality rates among males decreased significantly in most countries, including those of Europe and Asia, over the past decades. But rates continued to increase in several Eastern European countries, including Hungary and Slovakia. The increase in females in most European countries largely reflects the ongoing tobacco epidemic. This contrasts with the decreasing trends at all ages in both males and females in the United States and United Kingdom, where the tobacco epidemic began and declined earlier. However, incidence rates for oral cancer sites related to HPV infections, such as the oropharynx, tonsil, and base of the tongue, are increasing in young adults in the United States and in some countries in Europe, which is hypothesized to be in part due to changes in oral sexual behavior.56,57
2A.3 TREATMENT MODALITIES

Surgery and Radiotherapy are the only curative treatment options in the management of head and neck squamous cell carcinomas. Chemotherapy by itself usually fails to achieve good response rates, and cannot be considered as a definitive treatment. While single modalities of treatment can achieve excellent cure rates in early stage disease, the results in the advanced stages remain poor. Because of this, combined modality treatment strategies are often employed in higher stage disease. Factors such as age, sex, tumor site, tumor–lymph node–metastasis (TNM) stage and histologic grade may help to guide treatment decisions.⁵⁸

2A.3a Surgery

Surgery was the only available curative treatment option for head and neck malignancies, before the advent of radiotherapy. The principle of surgery is to resect the tumor en-bloc, with a margin, and to remove the potential sites harboring sub-clinical metastases; this usually involves neck dissections.

Surgery may be used as a single treatment modality in early disease (stage I and II). It is combined with radiotherapy in advanced disease (stage III and IV). The advantages of surgery compared with radiation therapy, assuming similar cure rates, may include:

(1) A limited amount of tissue is exposed to treatment

(2) Treatment time is shorter

(3) The risk of immediate and late radiation sequelae is avoided, and

(4) Irradiation is reserved for a subsequent head and neck primary tumor, which may not be as suitable for surgery.
2A.3b Radiotherapy

Radiotherapy forms the mainstay of treatment in a large number of patients with head and neck cancers, due to advanced, unresectable status of the disease at presentation. External beam radiotherapy and/or brachy-therapy are used as a single modality in early stage disease, or as a part of multimodality treatment in more advanced cancers.

Curative doses of radiotherapy generally involve 65-75 Grays (Gy) of irradiation to the gross disease, and 50 Gy or higher doses to the sites with suspected sub-clinical disease, with conventional fractionation of 1.8 to 2.25 Gy/setting. The treatment duration on an average is 6 to 7 weeks.

The advantages of irradiation as a primary treatment modality, over surgery, may include:

1. the risk of a major postoperative complication is avoided
2. no tissues are removed so that the probability of a functional or cosmetic defect may be reduced
3. elective irradiation of the lymph nodes can be included with little added morbidity, whereas the surgeon must either observe the neck or proceed with an elective neck dissection (sometimes bilateral depending on the primary site), and
4. the surgical salvage of irradiation failure is probably more likely than the salvage of a surgical failure.

Radiotherapy may be combined with surgery, either as a preoperative radiation or a postoperative radiation. More recently, chemotherapy has been increasingly combined with radiotherapy, in sequence (neo-adjuvant and/or adjuvant chemotherapy), or, more commonly, concurrently (concurrent chemo-radiotherapy; CCRT), based on the results of numerous trials that showed the superiority of the combined treatment.7-11
2A.3c Chemotherapy

Systematically designed randomized studies have established a role for drug therapy as part of the standard combined modality management of squamous cell head and neck cancer in several settings, including the therapy of unresectable disease, organ preservation strategies, and for patients with poor risk pathologic features after surgery. The rationale for CCRT is that chemotherapeutic agents may act as radiation sensitizers in addition to contributing their own anti-tumor effect. Also, effective chemotherapy may control micro-metastasis outside of the lesions treated with radiotherapy. Growing evidence indicates that more aggressive regimens showed an improvement in overall survival, disease-free survival, locoregional control of the disease, or a decrease in distant metastasis with CCRT compared to radiotherapy alone. Chemotherapy has been shown to improve the likelihood of disease control compared to irradiation alone in patients with advanced disease, albeit at the expense of increased acute toxicity, particularly within the radiation field. The results of the Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) evaluated randomized controlled trials published from 1965 through 1993, all of which compared locoregional treatment with or without chemotherapy. While the absolute improvement in 5-year survival overall in the whole group was 4% (P<.001), significant improvement appeared limited to those patients who received concomitant treatment (absolute difference of 8% at 5 years; p <.001). In contrast, the absolute survival difference seen at 5 years with induction (2%; P<.10) and adjuvant (1%; P = .74) chemotherapy treatment was not statistically significant. In conclusion, concurrent chemoradiotherapy is the standard of treatment presently for patients with advanced head and neck cancers.11
2A.3d General Guidelines for Selecting a Treatment Modality

In general, early stage disease has reasonably good survival rates with single modality treatment, and combination treatment is not used due to the increased toxicity out-weighing the potential benefit. Consequently, the choice of treatment is based on other factors, including age, co-morbidities and patient preference.

In contrast, higher stages have poorer outcomes, and are managed with multi-modality treatment strategies. Surgery may be combined with postoperative or pre-operative radiotherapy (with or without chemotherapy), and, in unresectable cases, concurrent chemotherapy is considered.17 Thus, treatment for locally advanced head and neck cancers in most cases is by concurrent chemotherapy and radiotherapy.19

2A.4 Mechanism of Radiation Effects upon Tissue

Biological effect begins with the ionization of atoms. The mechanism by which radiation causes damage to human tissue, or any other material, is by ionization of atoms in the material. Ionizing radiation absorbed by human tissue has enough energy to remove electrons from the atoms that make up molecules of the tissue. When the electron that was shared by the two atoms to form a molecular bond is dislodged by ionizing radiation, the bond is broken and thus, the molecule falls apart. This is a basic model for understanding radiation damage. Even though all subsequent biological effects can be traced back to the interaction of radiation with atoms, the two mechanisms by which radiation ultimately affects cells are direct and indirect effects.

2.4a Direct Effects

If radiation interacts with the atoms of the DNA molecule, or some other cellular component critical to the survival of the cell, it is referred to as a direct effect. Such an interaction may affect
the ability of the cell to reproduce and, thus, survive. If enough atoms are affected such that the chromosomes do not replicate properly, or if there is significant alteration in the information carried by the DNA molecule, then the cell may be destroyed by “direct” interference with its life-sustaining system i.e. by DNA damage.

2.4b Indirect Effects

If a cell is exposed to radiation, the probability of the radiation interacting with the DNA molecule is very small since these critical components make up such a small part of the cell. However, each cell, just as is the case for the human body, is mostly water. Therefore, there is a much higher probability of radiation interacting with the water that makes up most of the cell’s volume which leads to radiolytic decomposition of water in the cell. During the process of radiolysis the bonds that hold the water molecule together might break, producing free radicals such as hydrogen (H), hydroxyls (OH) etc. These free radicals may recombine or may interact with other fragments or ions to form compounds, such as water, which would not harm the cell. However, they could combine to form toxic substances, such as hydrogen peroxide (H₂O₂), which can contribute to the destruction of the cell. In the presence of oxygen, free radicals undergo further reactions to produce a relatively stable hydroperoxy radical and hydrogen peroxide that are more toxic to the biological structures.⁴³
CHAPTER II B

ORAL MUCOSITIS

AN OVERVIEW

An insight of Oral Mucositis is necessary before reciting particulars of the present research work. Therefore, this chapter endow with detailed description of oral mucositis including anatomy of oral mucosa and its blood supply, definition, sign and symptoms, epidemiology, risk factors, pathophysiology, assessment methods, consequences and current available treatment options. Also effects of Oral Mucositis on quality of life are explained in the end.
2B.1 ORAL MUCOSA

2B.1a Mucous Membrane

The mucous membranes (or mucosae; singular mucosa) are linings of mostly endodermal origin, covered in epithelium, which are involved in absorption and secretion. Mucous membranes line cavities that are exposed to the external environment and internal organs. They are at several places contiguous with skin: at the nostrils, the mouth, the lips, the eyelids, the ears, the genital area, and the anus. The mucous membranes and glands secrete thick sticky fluid called mucus. The term mucous membrane refers to where they are found in the body and not every mucous membrane secretes mucus. The secreted mucus traps the pathogens in the body, preventing any further activities of diseases. The mucosal membrane lining the oral cavity is called oral mucosa.

2B.1b Structure of Oral Mucosa

The lining mucosa of the oral cavity is covered by a stratified epithelium and three different types of oral mucosa are recognized. These reflect the functional demands put upon different regions of the oral cavity and are classified accordingly. Masticatory mucosa covers the gingiva and hard palate, regions that are subject to mechanical forces of mastication, causing abrasion and shearing. It consists of a keratinized epithelium that closely resembles the epidermis of the skin in its pattern of maturation, and is usually tightly attached to underlying structures by a collagenous connective tissue. Lining mucosa covers the remaining regions, except for the dorsal surface of the tongue, and provides an elastic, deformable surface capable of stretching with movements such as mastication and speech. It is covered with a stratified squamous epithelium that is non-keratinized and can vary considerably in thickness in different oral regions. Lining
mucosa is attached by a loose, elastic connective tissue to underlying structures. A similar non-keratinized tissue lines the human esophagus and uterine cervix. A *specialized mucosa*, with characteristics of both masticatory and lining mucosa, is found on the dorsum of the tongue. It has a surface consisting of areas of both keratinized and non-keratinized epithelium; these are tightly bound to the underlying muscle of the tongue. The various types of oral mucosa differ in their relative extent in the oral cavity.\textsuperscript{59} From measurements made by Collins and Dawes, it can be calculated that the masticatory mucosa represents approximately 25\%, the specialized mucosa (dorsum of tongue) approximately 15\%, and the lining mucosa approximately 60\% of the total surface area of the oral lining. Both the structure and the relative area of the different types of mucosa will influence the permeability of the oral lining.\textsuperscript{60}

2B.1c **Blood supply of oral mucosa**

The blood supply of oral mucosa is extremely rich and is derived from arteries that run parallel to the surface in the sub-mucosa or, when the mucosa is tightly bound to underlying periosteum and a sub-mucosa is absent, in the deep part of the reticular layer. These vessels give off progressively smaller branches that anastomose with adjacent vessels in the reticular layer before forming an extensive capillary network in the papillary layer. From this network, capillary loops pass into the connective tissue papillae and come to lie close to, but never enter, the basal layer of the epithelium. The concentration of capillaries in oral mucosa is much greater than in skin.\textsuperscript{59}
2B.2 ORAL MUCOSITIS

Since long decades studies in oncology have mainly focused about the effectiveness of various anticancer treatment modalities on tumor response and survival of the patients with cancer. With the progression of time several advancements have occurred from the radical ways of treatment like radical surgeries, radical radiotherapy etc. to the recent organ sparing procedures where specifically tumor involving tissues are only targeted. These advancements occurred to decrease the comorbidities associated with the earlier radical procedures. Parallel to this advancements have happened for the locoregional control of tumor, like concurrent chemoradiotherapy, postoperative RT/CCRT, simulated CCRT, IMRT etc. In this era of modern medicine where more focus is not only adding quantity to the life, but also improving the quality of life of cancer patients. Many adverse events happen during the course of cancer treatment which may be of acute onset or chronic onset, among these oral mucositis is reported as one of the most burdensome acute adverse event by the patients.61

2B.2a Definition

None of the literature has clearly defined the term mucositis. Terms mucositis and stomatitis has been used in literature interchangeably. Mucositis is nothing but an acute reactive inflammation of mucosal epithelium throughout the length of gastrointestinal tract occurred due to cancer treatment, when such inflammation of mucosal epithelium occurs in the oral cavity and oropharyngeal region it is called “oral mucositis”.62 It is most disturbing acute adverse event of patients receiving treatment for cancer. It can be caused by various chemotherapeutic agents or radiation therapy. Combining both these modalities i.e. concurrent chemoradiotherapy can cause increase in the incidence as well as early onset of mucositis.61,62
2B.2b Signs and symptoms

Signs of mucositis vary from simple erythematic appearance of the mucosa to the severe ulcerative, necrotic or hemorrhagic lesions with the progression of its grades. Symptoms of oral mucositis are characterized by mouth and throat soreness, pain, swallowing difficulty, lost or altered taste (dysgeusia), and excessive thick viscid secretions. The thick viscid secretion due to mucositis may lead to gagging nausea, vomiting, and loss of appetite, fatigue, weight loss and aspiration. The problem of excessive viscid mucous in oral cavity and oropharyngeal region is has been rarely reported but shown to be one of the most distressing symptoms for many patients with high grade mucositis. Pain associated with mucositis is severe enough that it not only interferes with the patient’s ability to chew, swallow and talk but also alters the concentration and sleep. All these factors significantly decrease patient’s quality of life in all the spheres including physical, emotional, functional and social domains.12,13
2B.2c Epidemiology

Incidence

Almost every patient receiving RT to head and neck region will experience one or another grade of mucositis during the course of therapy. Incidence of oral mucositis varies according to patients’ settings; in a review by Trotti et al overall incidence of oral mucositis in head and neck cancer patients receiving cancer treatment was 80% with 39% had severe grade 3-4 oral mucositis. The incidence varied from as high as 100% in patients treated with altered fraction RT to as low as 22% in patients treated with chemotherapy alone. The incidence of mucositis in patients receiving conventional RT and Concurrent Chemoradiotherapy was 97% and 89% respectively. Incidence of higher grades 3-4 was highest 57% in radiation with altered fraction schedules and almost negligible 0% in chemotherapy alone treated patients. In another review by Sonis et al. reported incidence of higher grades mucositis was about 42% (Total no. of patients 2206) in HNC patients. A recent study has reported overall incidence of oral mucositis in patients receiving concurrent chemoradiotherapy for locally advanced head and neck cancer was 100%. In these studies incidence of higher grade OM varied from 20%-47%.
2B.2d Risk Factors

The Risk factors associated with the development of oral mucositis mainly influenced by the type of malignancy and the cytotoxic therapy administered, but patient related factors also play a role in it.

TREATMENT RELATED

Chemotherapy Related

Treatment-related risk factors for developing the mucositis depend upon the type of anti-neoplastic modalities used for cancer treatment. These include specific chemotherapeutic drug, dose, schedule, and use of radiation therapy. All of these will affect the subsequent development (severity and duration) of mucositis. The relative risk of developing OM following many standard chemotherapy regimens is 40%; but it becomes 100% following high-dose radiotherapy as treatment for head and neck cancers. Furthermore, nearly all patients receiving high-dose chemotherapy with hematopoietic stem cell transplantation (HCST) are affected. A schematic of the relationship between different therapies and the risk of developing OM is shown in Figure E.

Figure E: Risk of developing oral mucositis according to type of anticancer treatment
There are many chemotherapeutic agents which can induce mucositis (Table 1). Approximately 40% -70% of patients treated with standard chemotherapy regimens can develop mucositis. In Fluorouracil and cisplatin treated patients, 90% developed mucositis. Etoposide and melphalan are particularly stomatotoxic. Even doxorubicin, vinblastine, taxanes, and methotrexate can commonly induce mucositis, while it is less common with asparaginase and carmustine. (Table A) The management strategies which combine different chemotherapeutic agents further increase the likelihood of mucositis.65,66

Table A: Major chemotherapeutic agents responsible for oral mucositis

<table>
<thead>
<tr>
<th>Alkylating agents</th>
<th>Anthracyclines</th>
<th>Antibiotics</th>
<th>Antimetabolites</th>
<th>Taxanes</th>
<th>Vinca alkaloids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulfan, Cyclophosphamide, Mechlorethamine, Procarbazine, Thiotepa</td>
<td>Daunorubicin, Doxorubicin, Epirubicin</td>
<td>Actinomycin D, Amsacrine, Bleomycin, Mithromycin, Mitomycin</td>
<td>Cytosine arabinoside, 5-Fluorouracil, Hydroxyurea, Methotrexate, 6-Mercaptopurine, Thioguanine</td>
<td>Docetaxel, Paclitaxel</td>
<td>Vinblastine, Vincristine, Vinorelbine</td>
</tr>
</tbody>
</table>

**Radiation Related**

Mucositis is more common with external beam radiotherapy involving the head and neck region (mainly oropharyngeal tissues) but the IMRT is associated with less severe mucositis. The severity of mucositis depends on the type of ionizing radiation, the volume of irradiated tissue, the dose per day, and the cumulative dose. With conventional fractionation (2 Gy/day, 5 fractions per week), patchy mucositis becomes evident during the third week of irradiation and progresses to confluent mucositis.

Radiation induced oral ulcers may appear after 3-4 weeks of treatment, and their evolution is progressive if radiation therapy is not stopped. The severity of oral mucositis is increased with use of altered fractionation in head and neck radiotherapy.67 Horiot et al described a 66.5% incidence of diffuse mucositis with hyper-fractionation (with no acceleration), as
opposed to 49% with conventional fractionation, in patients being treated for oropharyngeal carcinoma.\textsuperscript{68} Geara et al reported an incidence of 53\% of grade III and 22\% of grade IV mucositis in 186 patients with head and neck neoplasms: 43\% of them were treated with concomitant boost regimen and 57\% were treated with hyper-fractionation with no acceleration.\textsuperscript{69}

Mucositis is seen in >75\% of conventional HSCT patients receiving certain conditioning regimens that combine total body irradiation (TBI) and chemotherapy. But newer approaches for HSCT including mini-transplants have less frequency and severity of mucositis.\textsuperscript{70}

**PATIENT RELATED**

There are several patient related factors appear to increase the potential for developing mucositis, like age of the patient, pre-treatment oral health, oral care during treatment, existing mucosal damage, impaired immune status, and decreased salivary production etc. Any decrease in neutrophil count before therapy may result in an impaired ability to mount an adequate inflammatory response on the oral mucosa thus causing more OM.\textsuperscript{71-73} (Table 2)

**Table B:** Factors responsible for oral mucositis

<table>
<thead>
<tr>
<th>Patient-related</th>
<th>Treatment-related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Radiation therapy: dose, schedule</td>
</tr>
<tr>
<td>Age &gt; 65 years or &lt; 20 years</td>
<td>Chemotherapy: agent; dose, schedule</td>
</tr>
<tr>
<td>Inadequate oral health and hygiene practice</td>
<td>Myelo-suppression</td>
</tr>
<tr>
<td>Periodontal diseases</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Microbial flora</td>
<td>Immuno-suppression</td>
</tr>
<tr>
<td>Chronic low-grade mouth infections</td>
<td>Reduced secretory immunoglobulin A</td>
</tr>
<tr>
<td>Salivary gland secretory dysfunction</td>
<td>Inadequate oral care during treatment</td>
</tr>
<tr>
<td>Herpes simplex virus infection</td>
<td>Infections of bacterial, viral, fungal origin</td>
</tr>
<tr>
<td>Inborn inability to metabolize chemotherapeutic agents effectively</td>
<td>Use of antidepressants, opiates, anti-hypertensives, antihistamines, diuretics, and sedatives</td>
</tr>
<tr>
<td>Inadequate nutritional status</td>
<td>Impairment of renal and/or hepatic function</td>
</tr>
<tr>
<td>Exposure to oral stressors including alcohol and smoking</td>
<td>Protein or calorie malnutrition, and dehydration</td>
</tr>
<tr>
<td>Ill-fitting dental prostheses</td>
<td>Xerostomia</td>
</tr>
</tbody>
</table>
Various patient related factors are described in detail below

**Age/Gender:**

There is a conflicting picture with regard to the effects of age and gender on the susceptibility for developing mucositis. Generally, younger patients are more susceptible for OM due to more rapid epithelial mitotic rate or the presence of more epidermal growth factor receptors (EGFR) in the epithelium at the early age. On the other hand, the physiologic decline in renal function associated with aging may result in higher incidence of chemotherapy induced OM in older patients. Alternatively, impaired immune function could also be a causative factor, as hematological malignancies are prevalent in the young and immune-suppression is a consequence of the treatment of these disorders. Immune-competence also declines with age. This may leave the elderly susceptible to mucositis. However, it is difficult to compare the incidence in mucositis in children and adults due to distribution of underlying malignancy and intensity of their therapies. Some studies have indicated that females are at a higher risk of mucositis, but the available data is contradictory and inconclusive.

**Oral hygiene Status:**

Poor oral hygiene poses substantial risk for the development and progression of higher grades of mucositis. In the oral cavity various forms of microorganism are present like bacteria, viruses, fungi and protozoa. Amongst these are a number of opportunistic pathogens whose population is generally kept low in healthy mouth by the competition from the non-pathogens, lack of attachment sites and protective actions of salivary components. Any disruption or lesion of epithelia caused by cancer therapy leads to the appearance of new glycol-conjugate structures on the luminal surfaces which often provide ideal sites for the attachment of opportunistic
This in turn gives selective advantage to opportunistic pathogens over other oral bacteria and enables these pathogens to persist and proliferate in the oral region. Any damage or loss of structural integrity of epithelium, also facilitate the entry of microorganisms to the submucosa and their spread to the systemic tissues.

Both Gram-positive and Gram-negative bacteria cause significant secondary infections. Previously Gram-negative were considered to be the major problem but now Gram-positive species like streptococcus sp., staphylococcus sp. and other species poses an increasing risk due to difficulties in controlling their proliferation and spread. In addition fungal mainly Candida, and viral, mainly Herpes simplex, infections are also major factors.

**Mouth Dryness (Xerostomia):**

Patients with decreased salivary production (pre-treatment xerostomia) are at high risk of developing the mucositis. Normally salivary mucins form a layer over the oral epithelium and act as a physical barrier against bacteria and noxious environmental agents. Bioactive components of saliva like lactoferrin, lysozyme, secretory immunoglobulins, antiviral factors and defensins, further limit the ability of microorganisms or harmful compounds to interact with the epithelia. EGF and other mitogenic or motogenic factors in saliva may modulate normal epithelial cell metabolism, but possibly their actual function is facilitating the restitution, repair and regrowth of oral epithelium after the damage or trauma.

Chemotherapy and radiotherapy can independently cause a severe reduction in salivary production. If the output of mitogenic or motogenic factors in saliva are low, this may delay the restitution, repair and regrowth of the damaged mucosa. Failure to rapidly restore epithelial barrier integrity will allow opportunistic pathogens invasion. In addition, poor production of
mucins and antimicrobial/ antifungal factors further reduces the control over the opportunistic pathogens.\textsuperscript{72} Proliferation by pathogens and the release of bioactive/ cell modulating compounds trigger severe inflammation in the mucosa and greatly exacerbate the severity and duration of epithelial damage.\textsuperscript{88-90}

Many classes of drugs commonly prescribed to HNC patients (opioids, antidepressants, phenothiazines, anti-hypertensive, anti-histamines, diuretics, and sedatives) can result in xerostomia.\textsuperscript{88} Prior Radiotherapy for the oral cavity commonly results in permanent xerostomia. Both alcohol and tobacco are reported to impair salivary function. The absence of salivary mucin glycoproteins may result in the loss of the normal lubricating and detergent properties of saliva and impair the permeability of the oral mucous membranes. Xerostomia may lead to decrease in oral pH from normal of 7.0 to 5.5 or less. With the lowering of oral pH, the normal buffering mechanism for lactic acid is lost. Quantitative and qualitative changes in saliva following radiation therapy may predispose to bacterial and fungal overgrowth.\textsuperscript{89,90}

\textit{Host Immunity:}

For any injury/ inflammation to heal early a good immunity is must. Patients with low or compromised local or systemic immunity, like those having low baseline neutrophil levels are at increased risk of infection and mucositis. Also development of neutropenia during chemotherapy or radiation greatly increases the oral mucositis incidence. In addition, duration of mucosal healing depends, at least in part, on that of the recovery of immune function.\textsuperscript{71-73}
**Mucosal Integrity:**

Any physical damage or loss of integrity of mucosal epithelium due to any reason poses an increased risk of oral mucositis. The incidence and severity of mucositis are greatest in epithelia with high rates of cell proliferation and turnover due to their susceptibility to chemotherapy/radiation. Hence, mucositis occurs especially around sites of abrasion, cuts or irritation on the mucosa because of high cell production rate in the epithelium to facilitate the repair of localized damage. Localized inflammation and selective colonization of the sites by pathogens may be additional causative factors. The repair of ill-fitting dental prosthesis, elimination of periodontal disease and extraction of offending teeth combined with effective oral hygiene during therapy has been demonstrated to reduce the incidence and severity of mucositis.71-73
2B.2e Pathophysiology

Mucositis is nothing but the erythematous, erosive, inflammatory, and ulcerative lesions that occur in the mucosal lining of the entire gastrointestinal tract including mouth, pharynx, and oesophagus secondary to cytotoxic cancer therapy. When it occurs in the oropharyngeal region it is called as oral mucositis.

The mucosa of oropharyngeal region is primarily composed of stratified, squamous, non-keratinizing epithelium that protects the underlying fibrous connective tissue and organs against mechanical and chemical insult; it tends to bear the brunt of the effects of cancer therapy. Due to high turnover rates of these cells (i.e., cells life span is approximately 3–5 days and the whole epithelium is completely replaced every 7–14 days) they are highly vulnerable to the cytotoxic or proliferative-limiting effects of stomatotoxic chemotherapy and head and neck radiation therapy. In patients who receive radiation therapy to head and neck region, the non-keratinized epithelium of the floor of the mouth, bilateral buccal regions, labial region, tongue, and soft palate experience the inflammatory and ulcerative changes whereas in HSCT patients undergoing total body irradiation, the most prominent lesions occur within the direct portals of radiation. The regions in the mouth with slower cell turnover like gingiva, dorsal surface of tongue, and hard palate are rarely affected.

During the earlier times it was believed that the mucositis happens simply by the direct damage caused by chemotherapy and radiotherapy to the basal epithelial cell layers which in turn leads to loss of renewal capacity of the epithelium resulting in clonogenic cell death, atrophy and consequent ulceration. The scientific knowledge about the various molecular, cellular and tissue events that lead to mucositis is continuously evolving. So the initial model of mucositis being solely as an epithelium mediated event happening due to non-specific toxic effects of radiation or
chemotherapy failed to explain the role of other cells and the extracellular matrix in the submucosal region. With scientific advancement related to molecular basis, mucositis appears to be more complex mechanism than a simple pathway of epithelial damage.

Since latter half of 20th century lot of research has been done to find the patho-biological factors associated with oral mucosal injury due to cytoreductive therapy. Few researchers have proposed various models of cancer therapy related mucosal injury. In 2003, Duncan and Grant described that mucositis develops through three interlinked stages these are initial inflammatory phase, the epithelial degradation phase and the ulceration/bacterial phase.\textsuperscript{72} Sonis et al have pioneered the work related to postulating various models of explaining the mechanism of chemos and/or radiotherapy induced mucositis.\textsuperscript{91-93,64} In 1998, Sonis et al proposed a 4 phase model of oral mucositis as Inflammation phase followed by subsequent epithelial phase, Ulcerative/infective and healing phases.\textsuperscript{91} As the scientific knowledge regarding the mucositis improvised, in 2004 Sonis et al postulated a new continuously evolving working model of 5 phases of development of mucositis\textsuperscript{92,93,64} which has gained a wide appreciation in medical community. They postulated that mucosal barrier injury happens in 5 phases: initiation, up-regulation and generation of messenger signals, signaling and amplification, ulceration with inflammation, and finally, healing.\textsuperscript{92,93,64} (Figure F)
**Initiation**

This phase occurs shortly after the administration of cancer treatment, exposure to chemotherapeutic agents or radiation leading to generation of oxidative stress and reactive oxygen species (ROS) is considered as the initial events happening in the development of mucositis. Whether they are generated by chemotherapy or radiation exposure, ROS directly damage cells, tissues, and blood vessels. These ROS are nothing but normal by products of cellular metabolism within the cells that comprises the epithelium. These ROS can cause break in the DNA strands in the epithelium and submucosa hence initiate a cascade of other downstream biological events. The activation of ROS and their subsequent ability to stimulate a
number of transcription factors seem to characterize the acute tissue response to a stomatotoxic challenge and are considered the hallmark of the initiation phase of mucositis leading to other biologic events.64

**Up-regulation and generation of messenger signals**

During this phase, multiple events occur simultaneously. ROS cause DNA damage and subsequent clonogenic cell death in the epithelial layer. Due to exposure to chemotherapeutic agents or radiation numerous number of transcription factors are activated that affect a number of genes controlling protein synthesis and cell signaling. Out of these transcription factors involved, one of the most important is nuclear factor-kappa B (NF-κB), which controls nearly 200 genes involved with mucositis, including those encoding pro-inflammatory cytokines and cell adhesion molecules. The 26S proteasome associated with NF-κB, is detectable in stressed mucosa, it has the capacity to upregulate a large panel of genes with the potential to elicit a broad range of tissue responses, and it can respond differently to varying challenges. Once activated, NF-κB leads to the up-regulation of many genes, including those that result in the production of the proinflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin (IL) -1β, and IL-6. This leads to tissue injury and apoptosis. Increased synthesis of the cytokines IL-1β and IL-6 can also be seen in the mucosa. Upregulation of other genes causes the expression of adhesion molecules, subsequent activation of the cyclooxygenase-2 pathway, and consequent angiogenesis.64 (Figure G)

In addition other enzymes activated by radiation, chemotherapy, and ROS include ceramide synthase and sphingomyelinases that can increase the rate of apoptosis. The ceramide pathway may work in parallel or sequentially to induce primary apoptosis. Fibronectin break-up also occurs during the up-regulation and message-generating phase of mucositis. Macrophages
are activated subsequently, leading matrix metalloproteinases to then cause tissue injury directly or leading to more production of TNF-α. The end result of the second phase of mucositis is to trigger a variety of simultaneous events in all involved tissues at all levels that can be lethal to epithelial cells and surrounding fibroblasts. (Figure H)

**Figure G: Up-regulation and generation of messenger signals phase 1**

Chemotherapy (CT) or radiotherapy (RT) may initiate mucositis directly by causing DNA strand breaks, through the generation of reactive oxygen species (ROS), or through enzymatic or transcription factor activation in multiple cellular elements within the mucosa. ROS may damage other cells and tissues directly and also stimulate secondary mediators of injury, including such transcription factors as nuclear factor-κB (NF-κB). When messenger signals are up-regulated and generated, multiple events occur simultaneously. ROS cause DNA damage leading to clonogenic cell death. Activation of transcription factors in response to ROS, RT, or CT results in gene up-regulation, including the genes tumor necrosis factor-α (TNF-α) and the interleukins (IL-1β) and IL-6, leading to tissue injury and apoptosis of cells within the submucosa and primary injury of cells within the basal epithelium. Other genes also are up-regulated, leading to the expression of adhesion molecules, cyclooxygenase-2 (COX-2), and subsequent angiogenesis.
**Figure H: Up-regulation and generation of messenger signals phase 2**

During up-regulation and generation of messenger signals, enzymes (sphingomyelinase and ceramide synthase) that catalyze ceramide synthesis are activated directly by radiotherapy (RT) or chemotherapy (CT) or indirectly by reactive oxygen species (ROS) and tumor necrosis factor (TNF-α). The ceramide pathway provides an alternative conduit for apoptosis of both submucosal and basal epithelial cells. In addition, fibronectin breakdown leads to macrophage activation and subsequent tissue injury mediated by matrix metalloproteinase (MMP) and production of additional TNF-α.

**Signaling and amplification**

The third phase consists of feedback loops that further increase the number and level of activating signals. In this phase proinflammatory cytokines like TNF-α, not only cause direct damage to mucosal target cells but also amplify the mucosal injury initiated by radiation and chemotherapy by activating a number of pathways, including the ceramide and caspase pathways and the transcription pathway mediated by NF-κB that can further lead to tissue injury. These
signals lead to further production of the proinflammatory cytokines TNF-α, IL-11, and IL-6. In addition, activation of the ceramide pathway by TNF-α may provide an effector mechanism for secondary TNF-α-mediated tissue damage. The net result is an ongoing cycle of amplification of injury that persists well after the initial insult of radiation therapy or chemotherapy. Ultimately in the end the tissue is altered biologically, even though it may appear normal.64 (Figure I).

Figure I: Signaling and amplification phase

During the signaling and amplification phase, one consequence of the flood of mediators released in response to the initial insult is a series of positive feedback loops that serve to amplify and prolong tissue injury through their effects on transcription factors and on the ceramide and caspase pathways (not shown). Consequently, gene up-regulation occurs with resultant increases in injurious cytokine production. Because the damaging events are focused in the submucosa and basal epithelium, the clinical appearance of the mucosal surface remains deceptively normal.
Ulceration

The fourth phase of mucositis involves penetration through the epithelium into the sub-mucosa i.e. Ulceration. This phase is characterized by a robust inflammatory infiltrate comprised of both polymorphonuclear and round inflammatory cells. The ulcerated surface can then be colonized by gram-positive, gram-negative, and anaerobic bacteria.

**Figure J: Ulceration phase:** The ulcerative phase is the phase associated most consistently with mucositis. The injury and death of the basal epithelial stem cells resulting from the prior phases result in atrophic changes that culminate in true deterioration and breakdown of the mucosa. This phase generally is markedly symptomatic. The ulcer serves as a focus for bacterial colonization, particularly in an environment so rich in microorganisms. Secondary infection is common. What is significant is that cell wall products from bacteria penetrate the submucosa and further exacerbate the condition by stimulating infiltrating macrophages to produce and release additional proinflammatory cytokines. In neutropenic patients, whole bacteria may invade submucosal vessels to cause bacteremia or sepsis. IL: interleukin; TNF-α: tumor necrosis factor-α.

Cell wall products from bacteria can activate tissue macrophages, leading to further production of the proinflammatory cytokines TNF-α, IL-11, and IL-6 hence more damage.
Similarly, changes in the salivary composition and amount may influence the susceptibility of tissue to cytotoxic agents and the tissue’s ability to heal. The net results of this phase are further cytokine amplification, inflammation, and pain, and the patient is at increased risk for bacteremia and sepsis.64 (Figure J) This ulcerative phase is primarily responsible for the main clinical symptoms of mucositis (pain, inflammation, and loss of function) and is associated with higher costs (increased drug use and hospitalization).

**Healing**

This is the final phase of oral mucositis; healing starts with a signal from the extracellular matrix, leading to a renewal of epithelial proliferation and differentiation and re-establishment of the local microbial flora. Epithelial cells, under control of signals secreted by the extracellular matrix, migrate, grow, and differentiate to form a wound. These signals are then down-regulated to avoid hyperplasia. Depending on the clinical setting, other associated clinical events simultaneously return to normal. For example, in hematopoietic stem cell transplantation (HSCT), the healing phase also is marked by leukocyte recovery. After the healing phase, the oral mucosa appears normal; however, despite its normal appearance, the mucosal environment has been altered significantly. There is residual angiogenesis, and the patient is now at increased risk of future episodes of oral mucositis and its complications with subsequent anticancer therapy.64

Even though each of the phases is depicted as separate in the above model, it is likely that these stages overlap, occurring in a continuous, dynamic interaction. The mechanism explained for mucositis development is same for both chemotherapy and radiation only except that with chemotherapy phases happen earlier than radiation.64,66 In case of radiation, damages are seen after completion of 1-2 weeks i.e. accumulated dosages of radiation.66
2B.2f Assessment of Oral Mucositis

Mucositis must be assessed accurately for the development of effective new therapies. Mucositis measurement tools must precisely describe mucosal damage, reproducibly measure severity, objectively classify changes, and link underlying molecular mechanisms to clinically relevant outcomes such as improvement in ulceration or degree of pain reduction. There are a number of scoring systems that has been developed for the assessment of oral mucositis. But none has been proved to be of ideal standard having feasibility, reproducibility, reliability, validity, sensitivity and specificity for measuring mucositis in various clinical and research settings. None of the scales developed so far has been accepted universally for the assessment of mucositis. Regardless of the scale used, a systematic routine objective assessment of the oral cavity should be performed in all patients who are at risk of developing oral mucositis. In addition to the objective physical manifestations of mucositis (like erythema, ulceration and hemorrhage) there are subjective and functional manifestations of mucositis, like pain and swallowing difficulty (dysphagia) has to be assessed thoroughly. Any patient who will receive radiotherapy to the head and neck region should have a thorough assessment of the oral cavity before initiation of the therapy and at regular intervals during treatment. Various scoring systems used to assess the oral mucositis objectively and subjectively shown in Tables C1-C3 below.

Scoring of Oral Mucositis

Various terminologies have been used to describe mucosal injury, for example stomatitis or mucositis has been used interchangeably while describing the inflammatory oral conditions. Earlier days mucositis scales used most commonly were designed to define the stomatotoxicity resulting from different cancer treatments. There are four types of scales which have been developed to assess the oral mucositis.
First group of scales are mainly based on the WHO scale, which was developed to clinically assess the patients receiving the cancer treatment. These are simple, combined, variable toxicity scales comprised 4-5 point rating scales which rate the overall status of the mouth relative to the appearance of mucosa, pain severity, and, in some cases, functional limitations relative to patient’s oral status (e.g., the ability to eat/swallow). The National Cancer Institute-Common Toxicity Criteria (NCI-CTC) scales and RTOG scales comes under this group.64 (Table C1)

Table C1: Various scoring systems used to assess oral mucositis

<table>
<thead>
<tr>
<th>Scale (use)</th>
<th>Source</th>
<th>Elements measured</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCI-CTC (clinical and research)</td>
<td>Trotti et al., 2000 (see also <a href="http://ctep.cancer.gov/forms/CTCv20">http://ctep.cancer.gov/forms/CTCv20</a> 4-30-992.pdf41)</td>
<td>Combined elements: symptom (pain), signs (erythema, ulceration); function; type of dietary intake</td>
<td>Used widely in research and clinical care settings; specific scales for mucositis in patients undergoing head/neck radiation, chemotherapy, or HSCT</td>
<td>Research assessment potentially confounded by combination of symptoms, signs, and functional changes</td>
</tr>
<tr>
<td>WHO (clinical and research)</td>
<td>WHO, 1979</td>
<td>Combined elements: symptom (pain), signs (erythema, ulceration); function: type of dietary intake</td>
<td>Used widely in research and clinical care settings; specific scales for mucositis in patients undergoing head and neck radiation, chemotherapy, or HSCT</td>
<td>Research assessment potentially confounded by combination of symptoms, signs, and functional changes</td>
</tr>
<tr>
<td>RTOG (clinical and research)</td>
<td>RTOG (see <a href="http://www.rtog.org/members/toxicity/acute.htm">http://www.rtog.org/members/toxicity/acute.htm</a>)</td>
<td>Combined elements: symptom (pain), signs (unspecified); function: unspecified</td>
<td>Used widely in research and clinical care settings</td>
<td>Research assessment potentially confounded by combination of symptoms, signs, and functional changes</td>
</tr>
</tbody>
</table>

NCI-CTC: National Cancer Institute Common Toxicity Criteria; HSCT: hematopoietic stem cell transplantation; WHO: World Health Organization; RTOG: Radiation Therapy Oncology Group
**Second group** of scales has been evolved from the first group of scales and are mainly developed as nursing management and research tool. These scales combine objective, functional and symptomatic variables by applying them to specific anatomic sites, adding greater specificity with various aspects of oral function and subjective patient responses. Western Consortium of Cancer Nursing Research (WCCNR) scale comes under this category of scales.\(^6\) (Table C2)

**Table C2:** Various scoring systems used to assess oral mucositis

<table>
<thead>
<tr>
<th>Scale (use)</th>
<th>Source</th>
<th>Elements measured</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined objective/functional/symptom scales</td>
<td></td>
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<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Oral Assessment Guide (clinical)</td>
<td>Eilers et al. 1988</td>
<td>Signs (erythema), symptoms (pain, salivary changes), functional disturbances (swallowing, voice)</td>
<td>Global scale that can reflect clinical status/outcomes; suitable for nursing care decision making</td>
<td>Not all variables necessarily link with clinical status; some variables not continuous</td>
</tr>
<tr>
<td>Western Consortium for Cancer Nursing Scale (clinical)</td>
<td>Western Consortium for Cancer Nursing Research, 1991</td>
<td>Lesions, color, bleeding, subjective variables</td>
<td>Global scale that can reflect clinical status/outcomes; refined in 1998, based on elimination of five measures other than lesions, color, or bleeding</td>
<td>Mixed objective, subjective, and functional variables; difficult to score precisely</td>
</tr>
<tr>
<td>Tardieu Quantitative Scale of Oral Mucositis for HSCT (research)</td>
<td>Tardieu et al., 1996</td>
<td>Mucosal changes, salivary function, function (voice, swallowing), pain</td>
<td>Includes four anatomic sites, range of severity</td>
<td>Not validated (pilot study only); only tested in HSCT patients; detailed, requires moderate to significant training</td>
</tr>
<tr>
<td>Walsh Quantitative Scoring System for Oral Mucositis (clinical and research)</td>
<td>Walsh et al., 1999</td>
<td>Mucosal changes, functional changes, salivary function, pain</td>
<td>Conceptual elements of NCI or WHO scale applied to specific anatomic sites; moderate training</td>
<td>Not validated; only tested in HSCT patients</td>
</tr>
</tbody>
</table>
**Third group** of scales were designed mainly for the clinical research trial. These are detailed objective scoring scales, which tend to focus on directed, separately score, objective and subjective end points. Oral Mucositis Index (OMI) and Oral Mucositis Assessment Scale (OMAS) come under this category of scales.64 (Table C3)

**Fourth group** of scales has been developed for the in vitro measurement of mucositis. These scales are purely for research, for example Epithelial Viability Scale.64 (Table C3)

**Table C3: Various scoring systems used to assess oral mucositis**

<table>
<thead>
<tr>
<th>Scale (use)</th>
<th>Source</th>
<th>Elements measured</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMI for HSCT (research)</td>
<td>Schubert et al., 1992</td>
<td>Thirty-four mucosal changes: signs (atrophy, erythema, ulceration/ pseudo-membrane, edema, and selected sites); pain scores (separate VAS)</td>
<td>Specific to 11 oral anatomic sites, thereby permitting sub-analyses of changes across the oral mucosa; eliminates confounders of symptoms and functional disturbances; scores consistent with NCI and WHO scores</td>
<td>Requires more examiner experience and time than NCI-CTC and WHO scales; only tested in patients undergoing HSCT</td>
</tr>
<tr>
<td>Twenty-item OMI for HSCT (research)</td>
<td>McGuire et al., 2002</td>
<td>Twenty mucosal changes: signs (atrophy, erythema, ulceration/ Pseudo-membrane edema, and selected sites)</td>
<td>Specific to nine oral anatomic sites; clinical objective changes scored as in full OMI</td>
<td>Requires less expertise than OMI</td>
</tr>
<tr>
<td>OMAS for chemotherapy, radiation, and HSCT (research)</td>
<td>Sonis et al., 1999</td>
<td>Signs (erythema, ulceration)</td>
<td>Same advantages as OMI with fewer oral anatomic sites scored</td>
<td>Requires more examiner experience and time than NCI-CTC and WHO scales but less time than OMI</td>
</tr>
</tbody>
</table>

In vitro measurement

| Epithelial Viability Scale (research) | Wymenga et al., 1997 | Trypan blue-based exclusion, based on oral epithelial smears | Easily administered; in vitro objective measure; studied with both chemotherapy induced and radiation induced mucositis | Early in development; requires additional validation |

VAS: visual analog scale; OMI: Oral Mucositis Scale; OMAS: Oral Mucositis Assessment Scale.
First group of scales which are based on WHO design are the most relevant scales for clinical management of oral mucositis. A systematic review of approximately 400 trials, revealed that most of the studies utilized the NCI (43%) or WHO (38%) scales followed by a study-specific scale (10%), and a cooperative group (RTOG/ECOG) scale (5%). In this study we have used EORTC/RTOG scale for the assessment of oral mucositis.64

**World Health Organization Oral Toxicity Scale**

These were the first established guidelines proposed by the World Health Organization (WHO) in 1979 which were developed to clinically assess the oral toxicity in patients receiving the cancer therapy. The WHO Oral Toxicity Scale measures anatomical, symptomatic, and functional components of oral mucositis. The severity of the condition is graded from 0 (no oral mucositis) to 4 (alimentation not possible and the patient needs total parenteral nutrition).94

(Table D) This is one of the most widely used scale in various clinical and research settings. Easy to assess and less time consuming, reliability and validity not established.

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WHO Oral mucositis (stomatitis)</strong></td>
<td>None</td>
<td>Soreness ± erythema</td>
<td>Erythema, ulcers, and patient can swallow solid food</td>
<td>Ulcers with extensive erythema and patient cannot swallow solid food</td>
<td>Mucositis to the extent that alimentation is not possible</td>
</tr>
</tbody>
</table>

**National Cancer Institute- Common Toxicity Criteria**

In 1982, the National Cancer Institute (NCI) created the Common Toxicity Criteria (NCI-CTC) for the evaluation of CT-related effects. In 1997, the NCI revised the original CTC as NCI-CTC version 2.0.95 Later another revision of the NCI-CTC version 2.0 was done as NCI-CTC version 3.0 in April 30, 1999. This updated NCI-CTC version 3.0 was released in December 2003, for
widespread implementation. In 2009, NCI have again revised the toxicity criteria and a new NCI-CTC version 4.0 has been formulated, now it is used widely in cancer research. (Table E)

**Table E: National Cancer Institute- Common Toxicity Criteria**

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCI-CTC Chemotherapy-induced stomatitis/ pharyngitis (oral/pharyngeal mucositis)</strong></td>
<td>None</td>
<td>Painless ulcers, erythema, or mild soreness in the absence of lesions</td>
<td>Painful erythema, edema, or ulcers but eating or swallowing possible</td>
<td>Painful erythema, edema, or ulcers requiring IV Hydration</td>
<td>Severe ulceration or requiring parenteral or enteral nutritional support or prophylactic intubation</td>
<td>Death related to toxicity</td>
</tr>
<tr>
<td><strong>NCI-CTC Associated with HSCT (stomatitis/ pharyngitis, oral/pharyngeal mucositis)</strong></td>
<td>None</td>
<td>Painless ulcers, erythema, or mild soreness in the absence of lesions</td>
<td>Painful erythema, edema, or ulcers but swallowing possible</td>
<td>Painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support</td>
<td>Severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia</td>
<td>Death related to toxicity</td>
</tr>
<tr>
<td><strong>NCI-CTC Mucositis due to Radiation</strong></td>
<td>None</td>
<td>Erythema of the mucosa</td>
<td>Patchy, pseudo-membranous reaction (patches generally _ 1.5 cm in greatest dimension and noncontiguous)</td>
<td>Pseudo-membranous reaction (contiguous patches generally _ 1.5 cm in greatest dimension)</td>
<td>Ulceration and occasional bleeding not induced by minor trauma or abrasion</td>
<td>Death related to toxicity</td>
</tr>
<tr>
<td><strong>NCI-CTCAE v4.0</strong></td>
<td>None</td>
<td>Asymptomatic or mild symptoms; intervention not indicated</td>
<td>Moderate pain; not interfering with oral intake; modified diet indicated</td>
<td>Severe pain; Interfering with oral intake</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
<td>Death related to toxicity</td>
</tr>
</tbody>
</table>
The Radiation Therapy Oncology Group Scale

The Radiation Therapy Oncology Group (RTOG) developed the Acute Radiation Morbidity Scoring Criteria for the evaluation of RT effects (separate criteria were also developed for the late effects of RT). In 1997, The RTOG appointed a panel to revise the RTOG scoring criteria and the revised RTOG was incorporated into the NCI-CTC to produce version 2.0, which has been used in all NCI-sponsored clinical trials since March 1998. This RTOG scale is an integral part of the NCI-CTC version 2.0. The RTOG assessment scale has been shown to provide an effective measure of the mucosal toxicity of anticancer therapeutic regimens. The RTOG Acute Radiation Morbidity Scoring Criteria for mucous membranes measure only the anatomical changes associated with oral mucositis. Severity of oral mucositis is graded from 0 (no oral mucositis) to 4 (necrosis or deep ulceration present, with or without bleeding).98 (Table F)

Table F: The Radiation Therapy Oncology Group Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>RTOG</td>
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</tr>
<tr>
<td>Acute oral mucous membrane toxicity caused by radiation</td>
<td>No change over baseline</td>
<td>Injection, may experience mild pain not requiring analgesic</td>
<td>Patchy mucositis that may produce inflammatory Serosanguinitis discharge; may experience moderate pain requiring analgesia</td>
<td>Confluent, fibrinous mucositis, may include severe pain requiring narcotic</td>
<td>Ulceration, hemorrhage, or necrosis</td>
</tr>
</tbody>
</table>

Western Consortium for Cancer Nursing Research Scale

Western Consortium for Cancer Nursing Research (WCCNR) has been developed from the earlier scales for the nursing management and research. The revised oral mucositis staging system of the WCCNR is a 4-grade assessment tool that measures only the anatomical changes associated with oral mucositis.99 (Table G)
Table G: Western Consortium for Cancer Nursing Research Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCCNR</td>
<td>Lesions: none</td>
<td>Lesions: 1-4</td>
<td>Lesions: &gt; 4</td>
<td>Lesions: coalescing</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Color: pink</td>
<td>Color: slight red</td>
<td>Color: moderate red</td>
<td>Color: very red</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bleeding: none</td>
<td>Bleeding: N/A</td>
<td>Bleeding: spontaneous</td>
<td>Bleeding: spontaneous</td>
<td></td>
</tr>
</tbody>
</table>

Oral Mucositis Assessment Scale

Oral Mucositis Assessment Scale (OMAS) was developed by Sonis et al in 1999; this scale separates objective and subjective findings. Degrees of ulceration and redness measured in specific sites in the mouth were primary indicators of OM while oral pain, difficulty in swallowing, and the ability to eat were taken as secondary indicators. The OMAS provides an objective assessment of oral mucositis based on scoring of the presence and size of ulcerations or pseudo-membranes (score 0 to 3: 0 = no lesion; 1 = lesion < 1cm²; 2 = lesion of 1cm² to 3cm²; 3 = lesion > 3cm²) and erythema (score 0 to 2: 0 = none; 1 = not severe; 2 = severe) on the upper and lower lips, right and left cheeks, right and left ventral and lateral tongue, floor of the mouth, soft palate, and hard palate. (Table H) The OMAS has been shown to be highly reproducible between observers, responsive over time, and accurate in recording elements associated with mucositis. This scale is more quantitative for clinical research but may be difficult to use in routine clinical care.
### Table H: Oral Mucositis Assessment Scale

<table>
<thead>
<tr>
<th>Location</th>
<th>Ulceration*</th>
<th>Erythema†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Lower</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Left</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Tongue ventro-lateral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Left</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Palate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Hard</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
</tbody>
</table>

*0 = none; 1 = <1 cm²; 2 = 1–3 cm²; 3 = >3 cm²., †0 = none; 1 = not severe; 2 = severe.

### The Oral Mucositis Index

The Oral Mucositis Index (OMI) assesses the severity of oral mucositis in terms of erythema, ulceration, atrophy, and edema (each graded on a scale of 0 to 3, where 0 = none and 3 = severe). The OMI has been shown to be internally consistent with high test-retest and inter-rater reliability and exhibits strong evidence of construct validity.¹⁰¹

### 2B.2g Consequences of Oral Mucositis

Co-morbidities associated with severe oral mucositis

1. Severe pain which require use of opioid analgesics and anesthetics.
2. Swallowing difficulty due to soreness and/or ulcerations in mouth and throat, which sometimes may be severe enough that, necessitate total parenteral nutrition and rehydration.

3. Difficulty or inability to talk, which can hinder patient’s abilities to communicate.

4. Acute and chronic aspiration may happen due to excessive secretion of thick viscid mucous.

5. Increased risk of infection if oral hygiene is not maintained.

Consequences of all these may lead to interruption or modification in treatment plan which can result in poor loco-regional tumor control or sometime treatment failure. Because break in therapy allow healing of mucositis but also allow tumor regeneration resulting in poorer disease control. Also in some cases may require hospitalization and intensive supportive care, which along with aggressive narcotic pain management and invasive forms of nutritional support add significantly to the cost of the treatment program.

**Unplanned Treatment breaks/modification:**

The major limitation to more aggressive radiotherapy and concurrent CRT regimens is locoregional treatment-related toxicities, particularly mucositis and its consequences like aspiration, inanition, and severe pain. Mucositis may cause unplanned interruption or modification in main line cancer treatment i.e. radiation or chemotherapy regimen which in turn may lead to poor locoregional control of cancer and in turn treatment failure. A systematic review by Trotti et al. reported that the overall incidence of unplanned RT interruptions/modifications due to mucositis varied from 8%–27% and overall 11% had radiotherapy regimens modified because of mucositis. In another retrospective analysis of chart review of 434 patients treated by 154 oncologists, the incidence of unplanned RT breaks/delay due to severe mucosal toxicity among patients having mild, moderate and severe mucositis was 2.4%, 15.8%, and 46.8% respectively. Comparing patients having any OM with those without OM, the former were
found to be approximately 4-fold more likely to have had unplanned breaks in RT. Also corresponding estimates for unplanned breaks or delay in chemotherapy were 0.0%, 6.6%, and 25% respectively. Even in this study patients with oral mucositis were more likely to have had significant reductions in their chemotherapy dose. Comparing patients having any OM with those without OM, the former were 3.4 times more likely to have had breaks or delays in chemotherapy, 6.1 times more likely to have had their dose of chemotherapy reduced.67

**Feeding tube Insertion /Total Parenteral Nutrition (other than prophylaxis):**

In a review by Trotti et al. reported that the overall incidence of feeding tube insertion was 19% (819 patients), overall weight loss was 34% (880 patients) and weight loss ≥ 10% was 17% (485 patients).14 In a retrospective analysis by Vera-Llonch et al, more patients with OM required placement of feeding tubes or receipt of TPN (for reasons other than prophylaxis) (P < 0.009), and indwelling intravenous lines (P <0.013). Comparing between patients having any OM with those without OM, the former were nearly twice as likely to have received feeding tubes or TPN (for reasons other than prophylaxis) or indwelling intravenous lines.67

**Hospitalization**

In a review by Trotti et al. reported that the overall incidence of hospitalization due to mucositis in patients receiving standard RT, CRT and Altered fraction RT was 5%, 6% and 32 % respectively.14 In a retrospective analysis by Vera-Llonch et al approximately 33% of patients with severe OM were hospitalized compared with 16% of those with moderate OM, 21% of those with mild OM, and 11% of those with no reported OM (P <0.001). Comparing patients having any OM with those without OM, the former were more than 3 times as likely to have been hospitalized.67
2B.3 METHODS OF TREATMENT OF ORAL MUCOSITIS

There are several treatment modalities that have been tried for the prevention and management of mucositis but all have limited success rate. None of the modality has proved to be successful in prevention of mucositis, though few interventions proved to be effective in reducing the progression towards the higher grades. Many researches are undergoing to find a definitive preventive and treatment modality for the mucositis. Till now no gold standard of clinical practice has been set for the prevention and treatment of oral mucositis. Recently FDA has approved the Palifermin (recombinant growth factor) use for the prevention of mucositis in HSCT settings. At present the standard of care for mucositis is symptomatic management. Modalities targeting salivary production like Amifostine have been tried. To maintain oral hygiene various oral hygiene protocols has been formulated and various types of mouthwashes (alcohol and non-alcohol based) has been tried to reduce the incidence of mucositis. To reduce inflammation in mucosa various types of anti-inflammatory agents has been tried. To reduce the severity of pain various types of local as well as systemic analgesics and anesthetics has been tried. To reduce the opportunistic pathogens infection in mucosa various kinds of antimicrobial agents like antibacterial, antifungal as well as antiviral agents has been tried. Even modifications in standard treatment modalities of cancer (i.e. Radiation / chemotherapy) has been tried to decrease the occurrence of this severe adverse event.

The mucositis has become an important area in head and neck symptom research and formulating management guidelines. After intensive reviews of various clinical trials involving different modalities for the management of mucositis, various international organizations have published their recommendations for the management of oral mucositis. These include Multinational Association of Supportive Care in Cancer (MASCC)/ International Society of Oral
Oncoology (ISOO), National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO), European Oncology Nursing Society and a Cochrane review. Several strategies have been tried to prevent and treat the oral mucositis induced by cancer therapies.

2B.3a Preventive Strategies:

Basic oral Care/Maintaining Oral Hygiene:

The purpose of basic oral care is to reduce the impact of the oral microbial flora, reduce cancer therapy related symptoms of pain and bleeding, and prevent soft tissue infections that may have systemic effects. Maintaining a good oral hygiene is an important step in prevention of severe mucositis, as poor oral hygiene has been considered as an important risk factor for the development and progression of oral mucositis. Despite of limited evidence of benefits oral care protocols for the prevention of oral mucositis almost all reviews and clinical practice guidelines has recommended basic oral care is must as a best clinical practice. Rationale behind this is clear that good oral hygiene gives fewer portals to opportunistic pathogens to grow and hence prevents development of severe grades. Few authors have also suggested that patient should abstain from smoking and also avoid hot, spicy, and coarse foods, fruits and beverages with a high acid content, and alcohol (including alcohol-containing elixirs) as these cause mucosal irritation. Basic oral care protocol is a multidisciplinary approach which involves patient, family/caregivers, nurse physician, dentists, dental hygienist, dietician, pharmacist. It has been recommended that prior to initiating the cancer treatment in patients at risk of developing mucositis must require thorough evaluation of oropharyngeal region by a dentist. If any condition hampering mucosal health such as dental caries, periodontal disease, mucosal damage/sites of irritation has to be appropriately dealt with before starting the cancer treatment.
Maintaining a good oral hygiene before, during and after radiation therapy will reduce the risk for oral complications like infections, caries, gingivitis and osteo-radionecrosis. Basic oral care during radiation therapy involves gentle brushing with soft bristle toothbrush, dental flossing as tolerated and frequent oral rinsing with bland solution like normal saline with sodium bicarbonate and the use of moisturizing agents, regular dental evaluations and cleanings, and the use of lifelong daily dental fluoride prophylaxis. Alcohol based mouth rinses should not be used.\textsuperscript{16} A study by Bonnaure et al, demonstrated that tooth brushing reduced the number of oral lesions in patients receiving cancer chemotherapy. They also reported that using foam tooth brushes is not equivalent to tooth brushing and cannot be recommended for plaque control or caries prevention.\textsuperscript{107}

**Oral care protocols and patient education**

For the successful use of oral care protocol, patient, caregivers and professional staff education regarding the use of such protocols is also recommended. With the specific objective of reducing mucositis, Graham et al. initiated a unit-based oral care protocol and teaching program and documented a reduction in mucositis.\textsuperscript{108} Larson et al. used the PRO-SELF Mouth Aware Program in a study of outpatients receiving chemotherapy and demonstrated feasibility of the program in maintaining oral hygiene.\textsuperscript{109} To improve the consistency of oral care, Yeager et al. implemented an oral care standard in two inpatient hematology/oncology units and demonstrated feasibility, tolerability, and adherence in patients with leukemia and those undergoing transplantation.\textsuperscript{110} Improved oral status (i.e., reduced mucositis or increased oral comfort) was reported in three randomized clinical studies, and only one study reported no change in mucositis at the conclusion of the study.\textsuperscript{111-113} One randomized clinical trial did not show a statistically significant difference between controls and those undergoing the
intervention; however, participants who were taught the protocols performed oral hygiene routines more frequently compared with the control group and reported feeling more prepared to manage their symptoms.\textsuperscript{114}

2B.3b Palliative care (including Pain management)

Pain associated with mucositis is dependent on the degree of tissue damage, sensitization of pain receptors, and elaboration of inflammatory and pain mediators. Palliative care of mucositis and its associated pain is most important during head and neck radiation therapy. Systemic analgesics and other modalities, palliative mixture of agents (Magic or Miracle Mouthwashes), mucosal coating agents and topical anesthetics/analgesics has been used to decrease the mucositis associated pain.\textsuperscript{16}

Pain Management:

Reduction of pain associated with mucositis is an important aspect of symptoms management in patients receiving radiation treatment for head and neck cancer. Most of patients require both systemic as well as local analgesics. A recent study by Chen et al reported that only few HNC patients are given adequate narcotic analgesia. Dosage, frequency and duration of analgesics should be adjusted periodically to meet the pain intensity levels of patient.\textsuperscript{115} MASCC-ISOO strongly recommended the use of patient controlled analgesia with intravascular morphine sulphate for mucositis associated pain management in HSCT settings (even for pediatric population) but its use in chemotherapy and radiation settings is inconclusive. Few studies have reported use of transdermal fentanyl in patient having swallowing difficulty. The clinical practice guidelines given by World Health Organization\textsuperscript{116} and the Agency for Healthcare Research and Quality for managing acute pain\textsuperscript{117} should be followed while dealing with mucositis associated pain.
In 2002, Gelclair was approved by the FDA as a Class 1 medical device for the management and relief of pain associated with oral lesions of various etiologies, including oral mucositis or stomatitis, which may be caused by chemotherapy or radiotherapy. In an open-label study involving 30 patients, Gelclair appeared to be safe and effective in improving pain scores, swallowing endpoints, and nutritional endpoints.\textsuperscript{16}

**Topical preparations and other approaches:**

There are a number of topical agents that has been used alone or in combination for the management of mucositis and its associated pain. The most common ingredients used in combination include viscous lidocaine, benzocaine, milk of magnesia, kaolin, pectin, chlorhexidine, and diphenhydramine, while benzydamine and morphine has been used as single topical agents. But their effectiveness is inconclusive despite of the fact that they may be slightly better than normal saline. Regarding use of topical anesthetics (like lidocaine), their absorption through damaged mucosal surface is of great concern because of their cardiac effects.\textsuperscript{16}

**2B.3c RADIATION INDUCED MUCOSITIS**

The acute oral mucosal response to radiotherapy is a result of a sequence of biologic events that terminate in the death of epithelial cells. The threshold for mucositis seems to be about 20 Gy of standard fractionated radiotherapy. The cell cycle time of the basal keratinocytes is about 4 days, and because the epithelium is at least three or four cells thick, radiation changes begin to appear clinically at about 12 days after the start of irradiation. It seems likely that not all cells in the basal layer are equally radiosensitive. A pool of stem cells may determine the fate of radiated tissue. Clearly, additional investigation is warranted to define this process. Clinically, the oral mucosa may initially turn whitish followed by erythema and then after a few days more by a
patchy fibrinous exudate. If a high dose of radiation is given over a short time, ulceration may
develop early, with a thick fibrinous membrane covering the ulcers. Surviving keratinocytes
respond to radiation damage by dividing more rapidly, so that spontaneous complete healing can
be anticipated within 3 to 4 weeks of the end of radiation.

The degree of mucositis is determined by the treatment dose, radiation field size, and
fractionation schedules prescribed for individual patients and seem to be modified by saliva
volume, total epidermal growth factor (EGF) level, and the concentration of EGF in the oral
environment. Healing is impaired by high-dose radiotherapy and by tobacco smoking. Hyper-
fractionated radiation therapy and the combination of radiation and chemotherapy increase the
prevalence, severity, and duration of mucositis.\textsuperscript{16}

**Preventive strategies:**

Agents studied for their protective effects against radiation-induced mucositis include the
following.

**Methods to Reduce Exposure of the Mucosa to Radiation**

MASCC-ISOO recommended the use of midline radiation blocks and three-dimensional
radiation treatment. The rationale behind this is that due to midline radiation block and three-
dimensional radiation treatment lesser volume of normal oral mucosa will be exposed to
irradiation.\textsuperscript{118}

**Anti-inflammatory agents:**

*Benzydamine:*

MASCC-ISOO strongly recommended the use of benzydamine for the prevention of radiation-
induced mucositis in patients with head and neck cancer receiving moderate dose radiotherapy.
Benzydamine hydrochloride is a non-steroidal topical agent which has anti-inflammatory, analgesic, anesthetic, and antimicrobial properties. It has been used extensively in Europe and Canada as an intervention for mucositis. Benzydamine actively attenuates TNF-α production, inhibits NO (nitric oxide) production, has antimicrobial activity, and acts to stabilize cell membranes.

Benzydamine hydrochloride has been studied most extensively for the prevention and reduction of the severity of radiation-induced oral mucositis. Several small, double-blinded, randomized trials were reported in the 1980s. Two early studies suggested that benzydamine was effective in reducing the severity of the pain associated with oral mucositis. In a multicenter, randomized, double-blind, placebo-controlled clinical trial by Epstein JB et al involving head and neck cancer patients for the treatment of radiation-induced oral mucositis, demonstrated that benzydamine significantly reduced the incidence of erythema and ulceration and also delayed the need for systemic analgesics use compared with placebo. The study’s conclusions were based on cumulative radiation doses of 50 Grays (Gy) and the efficacy of the benzydamine with higher doses or with combination chemotherapy was not established. They also reported that Benzydamine was not effective in a small subgroup of patients who received accelerated radiotherapy (doses >220cGy/day).

It should be noted that benzydamine currently is not approved by the US Food and Drug Administration (FDA).

**Management strategies**

*Sucralfate:*

Updated MASCC-ISOO guidelines recommended that sucralfate not be used for the prevention of radiation-induced oral mucositis. Recent Cochrane database (2011) also reported insufficient
evidence regarding use of sucralfate for the treatment of radiation induced mucositis. Sucralfate is a non-absorbable aluminium salt of sucrose octasulfate that, when used as a rinse, is only 3% to 5% systemically absorbed. Sucralfate is a mucosal coating agent, evidence suggest no beneficial effects of it in radiation induced oral mucositis. A study by Etiz et al demonstrated the clinical and histo-pathologic reduction in radiation-induced oral mucositis with sucralfate. A study by Epstein JB et al using sucralfate suspension demonstrated that there was no reduction in radiation induced mucositis, but pain was significantly reduced. In another study by Dodd MJ et al showed no difference between micronized sucralfate and salt and soda mouth washes for the prevention of radiation induced mucositis in head and neck cancer patients.

**Coumarin/Troxerutine**

Few prospective randomized studies using Coumarin/troxerutine (Venalot Depot) showed a favourable effect in the treatment of radiation induced xerostomia, sialadenitis and mucositis.

**Antimicrobial Agents:**

Evidence suggests that radiation therapy causes changes in the normal oral flora and is associated with a marked increase in oral gram-negative bacteria and pseudomonas species. It has been believed that their presence could not only contribute to mucositis but also might result in the release of endotoxins that can cause adverse systemic effects. Homeostatic microbial communities may be protective in health by preventing or interfering with the colonization by exogenous pathogens (“colonization resistance”). When the oral tissues are irradiated, this colonization resistance is affected, and there are significant alterations in the oral micro-flora, which increase as salivary flow is disturbed. Oral levels of S. mutans, Lactobacillus species and Candida species typically increase significantly after radiotherapy to the head and neck. These
changes are maximal between 3 and 6 months after radiotherapy, after which time no further deterioration occurs, and, indeed, there is then sometimes a partial return toward the baseline flora.16

**Chlorhexidine**

MASCC-ISOO guidelines recommended that Chlorhexidine not be used for the prevention of oral mucositis in patients with solid tumors of the head and neck that are undergoing radiotherapy. Chlorhexidine is a broad-spectrum, topical antimicrobial agent. Few clinical trials using Chlorhexidine oral rinse consistently showed that it had no role in prevention of radiation induced oral mucositis in HNC patients.127-129 It may be used as oral care protocol due to its antifungal and antiplaque properties.

**Antimicrobial lozenge**

Updated MASCC-ISOO guidelines recommended that antimicrobial lozenge not be used for the prevention of radiation-induced oral mucositis. Evidence regarding use of antimicrobial therapy for the prevention of radiation-induced mucositis is conflicting. Various combinations of antimicrobial agents have been used in combination to prevent or decrease oral mucositis. Few studies selectively use antimicrobial agents targeting gram negative bacilli in oral flora:

Few clinical trials using polymyxin E, tobramycin, and amphotericin B in lozenges applied topically four times daily showed promising results.130 A study by Okuno et al containing combination of clotrimazole, bacitracin, and gentamicin, lozenges did not reduce radiation induced mucositis.131 Some studies have recommended gentamicin, vancomycin and nystatin combinations as an oral decontaminating rinse for prophylactic use, but further studies required to prove their use. A randomized trial by Symonds et al using antibiotic pastilles has shown a significant reduction in mucositis and weight loss during radiotherapy for head and neck
A trial by Wijers et al targeting Selective elimination of gram-negative bacteria of the oral flora did not result in a reduction of radiation-induced mucositis and, therefore, does not support the hypothesis that these bacteria play a crucial role in the pathogenesis of mucositis. A Meta-analysis by Sutherland and Browman suggested that only the narrow-spectrum antibacterial lozenges were effective. Two recent randomized trials by El-Sayed et al and Stokman et al of oral lozenges that contained bacitracin, clotrimazole, and gentamicin or polymixin, tobramycin, and amphotericin B showed no improvement in the incidence or severity of radiation-induced mucositis in head and neck cancer patients.

**Protegrin**

Protegrin is a naturally occurring peptide with broad-spectrum microbicidal activity has been used by some researchers for the prevention of mucositis. A study by Chen et al, demonstrated that use of a protegrin mouth rinse in patients radiated for oral cancer failed in modifying the course of mucositis.

**Biological Response Modifiers:**

Various growth factors have been utilized to reduce the incidence of mucositis.

**Granulocyte-macrophage colony stimulating factor (GM-CSF)**

Few early-phase trials with the topical application of GM-CSF showed beneficial effects on the incidence of oral mucositis. A study by Kannan et al, demonstrated that concurrent administration of GM-CSF with conventional fractionated radiotherapy in a consecutive series of patients, was associated with reduced mucositis incidence. But another study by Mascarin et al., using G-CSF did not find any beneficial effect on mucositis, though it reduced the number of treatment breaks. Another prospective randomized trial by Sprinzl et al demonstrated that topical application of GM-CSF has no beneficial effect on oral mucositis. A recent phase III
trial by Ryu et al of RTOG reported that subcutaneous granulocyte-macrophage colony stimulating factor (GM-CSF) failed to reduce oral mucositis in HNC settings. Overall, use of G- and GM-CSF is not recommended in patient receiving the radiation for HNC. Interleukin 1 is another growth factor suggested by Symonds et al may be effective for treatment of mucositis when provided in patients treated with hyper-fractionated radiation such as CHART. But it requires further studies to prove its efficacy in radiation induced mucositis.

**Cytoprotective Agents**

**Amifostine**

Amifostine and its active metabolite, WR-1065, supposed to act as free radical scavengers and also reduces pro-inflammatory cytokines. These can act as radio-protector for acinar cells of parotid gland exposed to radiation, hence indirectly may reduce the incidence of mucositis. A phase III trial by Brizel et al demonstrated intravenous administration of amifostine reduced the xerostomia levels significantly, but did not reduce mucositis. They also reported that Nausea, vomiting, hypotension, and allergic reactions were the most common adverse events. A recent meta-analysis by Sasse et al, of 1,451 patients has demonstrated statistically significant role in reducing the severity of oral mucositis in patients receiving RT with amifostine. However this reduction was at the cost of increased adverse effects associated with amifostine like nausea, vomiting, hypotension, and allergic reactions. The evidence of amifostine as a mucosal protectant is inconclusive. Amifostine has been approved in the United States for reducing the incidence of radiation induced severe xerostomia in HNC patients but has not been approved for oral mucositis. MASCC-ISOO and NCCN did not give any guidelines regarding the use of amifostine in radiation induced mucositis.

**Prostaglandins**
Some early studies reported beneficial effects of Topical prostaglandin E2 in prevention of radiation induced mucositis.\textsuperscript{146,147} Few early phase studies used silver nitrate to stimulate cells to divide to reduce radiation effects in normal tissue before radiotherapy, but results of this method are conflicting and require a controlled trial to prove its efficacy.\textsuperscript{148}

**Newer therapies:**

**N-acetyl Cysteine**

RK-0202 is a combination of the thiol antioxidant N-acetyl cysteine and a proprietary vehicle for trans-mucosal delivery. A recent phase II randomized trial by Chambers et al, demonstrated that RK-0202 significantly reduced the incidence of oral mucositis in HNC patients receiving radiation therapy.\textsuperscript{149} Further phase III controlled trial warranted to prove its efficacy in radiation induced mucositis.

**Other agents**

A study by Gujral et al demonstrated beneficial effects of Hydrolytic enzymes such as trypsin, papain, and chymotrypsin in the prevention of radiation induced mucositis in HNC patients.\textsuperscript{150}

**Zinc sulfate**

A placebo controlled randomized study by Ertekin et al (2004) found no statistically significant difference between zinc supplementation and placebo with regard to the prevention of radiation induced mucositis, but found a statistically significant difference in the prevention of moderate and severe grades mucositis.\textsuperscript{151} The other placebo controlled randomized study by Lin et al evaluating zinc sulfate reported that there was no statistically significant difference between the groups for the prevention of radiation induced mucositis.\textsuperscript{152} There is conflicting evidence from these two studies and more research is necessary to determine whether zinc supplementation is better than placebo with regard to the prevention of mucositis.
**Radiation: morning versus afternoon**

Two recent trials by Bjarnason et al\textsuperscript{153} and Goyal et al\textsuperscript{154} with a total of 428 patients, compared radiotherapy delivered in the morning vs radiotherapy in the evening, in head and neck cancers patients. One of these studies by Bjarnason et al\textsuperscript{153} had high risk of bias and the other study by Goyal et al\textsuperscript{154} was assessed as being at unclear risk of bias. No evidence of a difference was found for the prevention of severe mucositis from the two studies, or for the prevention of moderate plus severe mucositis.

**2B.2d CHEMORADIOThERAPY-INDUCED MUCOSITIS**

Almost every patient receiving HSCT experience oral mucositis and about two thirds develop severe mucositis (WHO grade III or IV). Mucositis starts developing around 5 days after HSCT infusion and persists for 2 to 3 weeks. By around 9 to 14 days after HSCT, basal cell regeneration occurs, and the mucositis improves. The only independent risk factor identified for mucositis is the conditioning regimen: high-dose melphalan (HDM) regimens exceed busulfan, busulfan-cyclophosphamide, cyclophosphamide-total body irradiation (TBI), cyclophosphamide-carmustine (BCNU), and cyclophosphamide-etoposide-carmustine.

Mucositis in these patients causes pain, restricts eating, is a portal of entry for infection, and is typically severe and prolonged with ulceration. More than 50% of patients require potent opiate analgesia to reduce pain for a median of 6 days.

**Anti-inflammatory Agents**

A preliminary study by Cohen et al demonstrated that prophylactic use of 0.1% topical tretinoin (anti-inflammatory) cream daily from the beginning of the HCST conditioning until marrow
engraftment in HSCT patients may reduce the objective and subjective symptoms of oral mucositis.155

Antimicrobial Agents

Chlorhexidine found to be little effective in prevention of mucositis.156 Loury et al reported that IB-367 is an antimicrobial peptide proved to be effective for oral mucositis in animal (hamster) model controlled clinical trials are recommended for their effectiveness in human subjects.157 Bondi et al demonstrated that topical use of antimicrobials lozenge containing amphotericin, polymixin, and tobramycin for oral mucositis, beneficial effects in pediatric patients undergoing BMT.158 But a RCT by Wijers et al did not show any significant benefit.133

Povidone-iodine

Few single center trials demonstrated that the use of povidone-iodine oral rinse along with standard prophylaxis for chemoradiotherapy induced oral mucositis can significantly reduce its incidence, severity, and duration.159,160 However, a RCT by Vokurka et al161 found no significant differences between the groups in respect of mucositis characteristics, fever of unknown origin and other infections between patients using povidone iodine and normal saline mouthwashes.

Pentoxifylline

MASCC-ISOO guidelines did not recommend the use of Pentoxifylline to prevent mucositis in patients undergoing HSCT. Pentoxifylline is a xanthine derivative. Few non randomized studies utilizing Pentoxifylline to prevent mucositis in patients undergoing HSCT demonstrated no beneficial effects in reducing the treatment related toxicities including oral mucositis.162,163 Two well controlled randomized trials by Attal et al164 and Clift et al165 also demonstrated that pentoxifylline failed to prevent the development of mucositis in patients undergoing HSCT.

Biologic Response Modifiers
Granulocyte-macrophage colony stimulating factor (GM-CSF)/G-CSF

MASCC-ISOO updated guidelines did not recommend the use of GM-CSF mouthwashes for the prevention of oral mucositis in patients undergoing HSCT. Few initial studies including a phase III trial demonstrated preventive effects of GM-CSF and G-CSF on mucositis in HSCT patients, but other studies showed less benefit during their topical application. A controlled trial by van der Lelie et al. found no beneficial effect on oral mucositis in patients undergoing HSCT by topical use of 300 µg GM-CSF dissolved in a 2% methylcellulose gel compared with a 2% methylcellulose gel alone. Two another double blind placebo controlled trials by Valcarel et al and Dazzi et al demonstrated no beneficial effect of using GM-CSF mouthwashes in reduction of incidence and duration of severe oral mucositis in patients undergoing HSCT. A non-randomized phase II trial by Mantovani et al demonstrated that local use of GM-CSF for prophylactic or curative purpose in advanced HNC patients receiving chemo- and chemoradiotherapy showed beneficial effect in reduction of incidence and duration of severe oral mucositis when it was used as prophylactic than curative purpose.

Keratinocytes growth factor (KGF) - Palifermin

MASCC-ISOO updated guidelines strongly recommended the use of palifermin (KGF1) at a dose of 60µg/kg per day for 3 days, prior to conditioning treatment and for 3 days post-transplantation for the prevention of oral mucositis in patients with hematologic malignancies, who are receiving high-dose chemotherapy and total body irradiation with autologous stem cell transplantation.

Palifermin is a recombinant human Keratinocytes Growth Factor-1 (Fibroblast Growth Factor 7) produced in Escherichia coli. Palifermin has multiple mechanisms of action, including down-
regulation of pro-inflammatory cytokines; inhibition of epithelial cell DNA damage and apoptosis; and stimulation of epithelial cell growth, differentiation, and migration.

KGF has shown beneficial effects on mucositis in animal models given chemoradiotherapy and in human HSCT patients receiving BCNU, etoposide, cytosine arabinoside, and melphalan, and in addition some beneficial effects on graft-versus-host disease has been described.¹⁷²,¹⁷³ A randomized phase I study by Meropol et al having a placebo control demonstrated that prophylactic intravenous administration of palifermin 3 days prior to each chemotherapy cycle with doses ranged from 1µg/kg per day to 80µg/kg per day in 6 different cohorts, beneficial effect on oral mucositis compared to placebo. They also reported that the palifermin was tolerated well in biologically active doses.¹⁷⁴ A placebo controlled study by Spielberger et al¹⁷⁵ demonstrated that in hematological cancer patients’ intravenous administration of palifermin for three consecutive days prior to initiation of conditioning therapy and after autologous HSCT, significantly reduced the incidence and duration severe oral mucositis compared to placebo group. They also reported significant reduction in, patient-reported soreness of the mouth and throat, the use of opioid analgesics, and the incidence of use of total parenteral nutrition. A recent multicenter study by Langner et al¹⁷⁶ demonstrated that palifermin significantly reduced the incidence and duration of oral mucositis in allogeneic stem-cell transplantation recipients compared to retrospective control leukemia patient. They also reported lesser use analgesics and total parenteral nutrition in these patients. Adverse effects associated with palifermin included skin reactions (rash, erythema, edema, and pruritus), oral reactions (dysesthesia, tongue discoloration, tongue thickening, dysgeusia), and arthralgia. FDA has already approved the use of Palifermin in HSCT patients receiving conditioning therapy.
In head and neck cancer patients receiving chemoradiotherapy few recent trials has proved efficacy of palifermin in prevention of oral mucositis. A Phase II multicenter, randomized, double-blind, placebo controlled trial by Brizel et al\textsuperscript{177} demonstrated that in HNC patients who received standard or hyper-fractionated radiotherapy with concomitant chemotherapy, intravenous administration of palifermin reduced the incidence and duration of mucositis compared with the placebo. A prospective randomized, placebo controlled trial by Henke et al\textsuperscript{178} demonstrated that in postoperative HNC patients receiving chemoradiotherapy, weekly administration of palifermin 120 µg/kg significantly reduced the incidence of severe oral mucositis 51% compared to placebo 67%. Another randomized, placebo controlled study by Le Q-T et al\textsuperscript{179} demonstrated that in patients receiving definitive chemoradiotherapy for locally advanced head and neck cancer, administration of 180 µg/kg prior to initiation chemoradiotherapy and then once weekly for 7 weeks significantly delayed the time of onset (35 days vs 47 days) and duration (5 days vs 26 days) of severe mucositis compared to placebo. They also reported adverse effects like rash, flushing, and Dysgeusia with palifermin use.

**Human keratinocyte growth factor 2 (KGF-2; repifermin)**

A multicenter phase II trial by Rockville involving patients with various malignancies who received conditioning regimens with chemotherapy before undergoing autologous HSCT demonstrated that repifermin significantly reduced the incidence of Grade II-IV oral mucositis.\textsuperscript{180} A phase I/II randomized trial by Freytes et al reported that repifermin significantly reduced oral mucositis in the HSCT setting compared with historic controls in phase I, but in phase II Human KGF2 2 has been withdrawn from study because of poor performance. This growth factor requires well-designed, randomized, controlled trials to prove its beneficial effects on oral mucositis.\textsuperscript{181}
**Interleukin 11 (IL-11)**

Beneficial effects of IL 11 on mucositis have been reported in animal models.\(^{182}\) A single human study by Sonis et al in HSCT using recombinant IL-11 at 50µg/kg showed a reduction in mucositis, but there is the potential for cardiac arrhythmias and edema.\(^{183}\)

**Cytoprotective Agents**

**Prostaglandins**

An uncontrolled patient cohort by Matejka et al reported that local application of prostaglandin E2 was found beneficial in chemoradiotherapy induced oral mucositis.\(^ {184}\) Well controlled studies have yet to be reported to prove its efficacy.

**Amifostine**

Altman and Hoffmans(1999) reported that intravenous administration of amifostine before each radiation treatment seems to have an impact on short-term toxicity of radio-/ chemoradiotherapy in HNC patients, allowing for a better adherence to the planned radiation time schedule, although the impact on mucositis is poorly documented.\(^ {185}\) A phase II trial by Suntharalingam et al demonstrated that in cancer patients treated with concurrent chemoradiotherapy, use of amifostine reduced the treatment-related toxicities, including oral mucositis.\(^ {186}\) A recent phase III randomized placebo-controlled study by Buentzel et al demonstrated that either intravenous or subcutaneous administration of amifostine during chemoradiotherapy for head-and-neck does not change the incidence of mucositis and though late toxicity xerostomia was higher during first year post CRT in subcutaneous administered patients.\(^ {187}\)

**Glutamine**

Glutamine is an amino acid, which is involved in protein and nucleic acid synthesis. Two studies by Anderson et al demonstrated mixed results with the use of oral glutamine. One group showed
reduction in the severity and duration of oropharyngeal mucositis in autologous HSCT patients but not in allogeneic HSCT patients, this may be because of the interaction with methotrexate.\textsuperscript{188,189} A trial by MacBurney et al. reported that parenteral administration of glutamine resulted in reduction in the severity and duration of mucositis in HSCT,\textsuperscript{190} while Schloerb et al have found no benefit from intravenous administration of glutamine in HSCT.\textsuperscript{191} In a subgroup of patients who were scheduled for HSCT and who underwent conditioning regimens with high potential for inducing mucositis, oral triclosan reportedly decreased the incidence and duration of ulcerative oral mucositis.

\textbf{2B.2e CHEMOTHERAPY-INDUCED MUCOSITIS}

It may be possible that the cellular events causing chemotherapy induced mucositis are similar to those for radiation, although in some instances, the pathways might vary. For example, if epithelial apoptosis is a consequence of activation of the ceramide pathway, it is possible that chemotherapy might act by means of ceramide synthase; whereas radiation induced injury is a consequence of sphingomyelinase activation. Whatever may be the cause once the process is initiated, the downstream events are likely to be similar.

Till now various types of modalities have been attempted for the prevention and treatment of chemotherapy-induced mucositis, but none works consistently. A recent Cochrane review (2011) of randomized controlled trials in this area concluded that ice chips were the only regimen of proven value.\textsuperscript{15} However, agents tested include the following.

\textbf{Methods to Reduce Exposure of the Mucosa to Chemotherapeutic Drugs}

\textit{Cryotherapy (Ice Chips) with 5 FU}
MASCC-ISOO guidelines recommend that patients receiving bolus 5-FU chemotherapy should undergo 30 minutes of oral cryotherapy to prevent oral mucositis. There is a conclusive evidence that ice chips used for 30 minutes before bolus administration of 5-FU prevents mucositis. The mechanism of action is thought to be by mucosal cooling, leading to vasoconstriction of mucosal vessels and consequent reduction in exposure of mucosal tissues to the chemotherapy agent, which may be a useful approach for agents with a short half-life.

Cochrane database review in 2000 by Clarkson, Worthington and Eden out of the 27 usable studies 14 had data for mucositis comprising 945 randomly assigned patients and 15 included data for oral candidiasis with 1164 randomly assigned patients, but only ice chips prevented mucositis. Studies by Dumontet et al and Meloni et al also reported some benefit from ice chips in patients treated with methotrexate or melphalan. A recent Cochrane review by Worthington et al confirmed the same findings. One randomized non-blinded study by Mahood et al reported that in patients who were receiving bolus 5-FU oral cryotherapy exhibited a reduction of approximately 50% in mucositis. In this study mucositis was evaluated by questionnaire. A randomized controlled trial by Casciu et al confirmed the same oral cryotherapy exhibited a reduction of approximately 50% in mucositis. Another randomized trial by Rocke et al of oral cryotherapy for either 30 minutes or 60 minutes reported that extending the duration of oral cryotherapy did not provide additional benefit; therefore, 3-minute cryotherapy was recommended.

**Cryotherapy with edatrexate**

MASCC-ISOO guidelines suggest using 20–30 minutes of oral cryotherapy in an attempt to decrease mucositis in patients who are treated with bolus doses of edatrexate. Few phase I and II trials by Edelman et al, Gandara et al and Dreicer et al (ECOG study) reported that oral
cryotherapy may reduce oral mucositis related to edatrexate. The rationale for its use is that edatrexate has the short serum half-life. Baydar et al\textsuperscript{201} reported that oral cryotherapy may not be useful in preventing oral mucositis in patients who are receiving 5-FU by continuous infusion or who are undergoing administration of such agents as methotrexate, doxorubicin, or other agents with long serum half-lives.

**Propantheline**

A study by Ahmed et al\textsuperscript{202} reported that propantheline may reduce mucositis induced by etoposide. A phase II trial by Oblon et al\textsuperscript{203} reported that use of propantheline in patients receiving high-dose chemotherapy (ifosfamide, carboplatin, etoposide) plus autologous HSCT dramatically reduced mucositis, presumably by reducing the topical exposure of the oral mucosa to drug in saliva. A well designed cross-over study by Awidi et al\textsuperscript{204} reported that use of oral pilocarpine reduced the chemotherapy-induced oral mucositis. Further studies are required to prove their efficacy.

**Anti-inflammatory Agents**

Wild Chamomile (Matricariarecutita L.) contains a number of anti-inflammatory compounds. A single case report by Mazokopakis et al\textsuperscript{205} using Chamomile mouthwash in methotrexate induced mucositis demonstrated some success but a controlled trial by Fidler et al,\textsuperscript{206} demonstrated that Chamomile mouthwash was ineffective in 5-FU–induced mucositis.

**Antimicrobial Agents**

**Chlorhexidine**

MASCC-ISOO guidelines recommend that chlorhexidine not be used to treat established oral mucositis. A study by Levy-Polack et al\textsuperscript{207} in children with acute leukemia, demonstrated that a daily preventive protocol consisting of (1) elimination of bacterial plaque; (2) application of a
mouthwash with a nonalcoholic solution of chlorhexidine 0.12%, and (3) topical application of iodo-povidone, followed by “swish and swallow” with nystatin, 500,000 units, results in a significant improvement in oral hygiene and reduction in the incidence of grade II oral mucositis and candidiasis. A well designed, multicentre randomized trial by Dodd et al,\textsuperscript{208} using 3 commonly used mouthwashes to treat chemotherapy induced mucositis demonstrated that Chlorhexidine was no more effective than water at reducing mucositis. They also suggested that salt and soda mouthwash is equally effective as Chlorhexidine or a mouthwash containing mixture of lidocaine, Maalox, and Benadryl at reducing mucositis.

A Cochrane database report in 2000 by Clarkson et al\textsuperscript{192} reported that for patients with cancer receiving chemotherapy (excluding head and neck cancer) prophylactic use of antifungal agents that are absorbed or partially absorbed from the gastrointestinal tract (e.g. fluconazole) reduce the clinical signs of oral candidiasis and systemic infection, and the partially absorbed drugs may be more effective. Systemic amphotericin B or fluconazole are commonly used for prophylaxis in high-risk patients during treatment of hematologic malignancies and HSCT. A review by Donnelly et al\textsuperscript{209} regarding role of antimicrobial agents in prevention and treatment of oral mucositis reported that no clear outcomes have been found with respect to the use of chlorhexidine, clindamycin, fluconazole, Iseganan, povidone iodine or combinations thereof.

Protegrin antimicrobial peptides act against gram-positive and gram-negative bacteria and yeasts. A study by Loury et al\textsuperscript{210} using one protegrin analog, IB-367 in animal models, showed moderate reduction of mucositis. But a phase III study by Chen et al\textsuperscript{211} protegrin did not show any beneficial effect on mucositis in myelo-ablated patients, in which the presence or absence of any inflammation was the end point.
Acyclovir

MASCC-ISOO guidelines recommend that acyclovir and its analogues not be used routinely to prevent mucositis. Few clinical trials in 1980s by Anderson et al\textsuperscript{212} and Saral et al\textsuperscript{213} reported that Acyclovir prophylaxis was effective in reducing herpes simplex virus (HSV) infection in patients with leukemia or lymphoma, but oral mucositis still develops in patients routinely receiving acyclovir or one of its prodrugs for prophylaxis. This suggests that HSV infection plays little or no role in causing oral mucositis.

Biologic Response Modifiers

**GM-CSF/ G-CSF**

A preliminary clinical study by Ibrahim and al Mulhim\textsuperscript{214} reported that use of GM-CSF and G-CSF mouthwashes ameliorate mucositis. Chi et al\textsuperscript{215} reported that GM-CSF may reduce the severity and duration of chemotherapy-induced oral mucositis after 5-FU, cisplatin and leucovorin chemotherapy, in HNC patients. Another non blinded study by Rosso et al\textsuperscript{216} have confirmed this finding. Few clinical trials reported that subcutaneous administration of GM-CSF from days 5 to 14 of chemotherapy appears to reduce the severity and duration of mucositis in patients treated with Vinorelbine (Navelbine) and carboplatin, or cyclophosphamide, doxorubicin and etoposide, or methotrexate, vinblastine, adriamycin, and cisplatinum.\textsuperscript{217-219} A study by Sprinzl et al\textsuperscript{220} reported that local application of GM-CSF may have some beneficial effects in chemotherapy induced mucositis.

**Transforming Growth Factor- β (TGF-β3)**

A study by Sonis et al\textsuperscript{221} involving animal models suggested that transforming growth factor- β (TGF-β3) can modulate cell cycling and attenuate 5FU induced oral mucositis. They demonstrated that topical application of TGF-β3 to the buccal mucosa in a hamster model
significantly reduced basal cell proliferation, as measured by proliferating cell nuclear antigen (PCNA) immunohistochemistry and DNA ploidy, and significantly reduced the severity of mucositis with respect to time, reduced weight loss, and increased survival. A Phase-I study by Wymenga et al\textsuperscript{222} reported that TGF-β3 (TGF-β3; CGP 46614) mouthwashes were well tolerated in preventing chemotherapy-induced mucositis. To prove efficacy of TGF-β in humans requires well designed recommended.

\textit{Epidermal growth factor (EGF)}

In another animal model study by Sonis et al\textsuperscript{223} reported that administration of EGF at the time of chemotherapy increased the severity of mucositis in hamsters.

\textit{Palifermin}

One study by Rosen et al\textsuperscript{224} suggested that palifermin may be useful in a dose of 40µg/kg/day for 3 days for prevention of oral mucositis in patients receiving bolus 5-FU plus leucovorin. Another trial by Schmidt et al,\textsuperscript{225} reported beneficial effects of palifermin for the prevention of high-dose methotrexate-induced oral mucositis. Another randomized trial by Vadhan-Raj et al\textsuperscript{226} reported the efficacy and safety of single-dose palifermin (180 µg per kg body weight) administered 3 days before each chemotherapy cycle in reducing oral mucositis during multi-cycle chemotherapy regimens for sarcoma. This dosing schema reduced the incidence and severity of oral mucositis and was well tolerated overall, although most subjects developed thickening of the oral mucosa. Future research is needed to delineate whether palifermin-associated reduction in oral mucositis will enhance adherence to chemotherapy regimens.

\textbf{Cytoprotective Agents}

\textit{Prostaglandins (PGE2)}
Few uncontrolled clinical studies demonstrated that topical prostaglandin E2 has some beneficial effect in chemotherapy induced mucositis. A double-blind study by Labar et al demonstrated no beneficial effects of PGE2 on oral mucositis in BMT patients.\textsuperscript{227}

\textbf{Vitamin E}

Vitamin E has an antioxidant effects. Few small placebo-controlled double-blind studies by Wadleigh et al\textsuperscript{228} and Lopez et al\textsuperscript{229} has shown that topical vitamin E effectively reduce the chemotherapy induced mucositis.

\textbf{Amifostine}

A retrospective study by Capelli et al\textsuperscript{230} reported that Amifostine may ameliorate mucosal damage after high-dose melphalan conditioning for peripheral blood progenitor cell auto-transplant. However, the dose required seems to be greater than that used for salivary gland protection, and tolerance caused by nausea is of considerable concern. Further studies required to prove its efficacy and to assess the side effects associated with potential mucosal protection and to confirm a lack of effect on tumor protection at higher doses.

\textbf{Glutamine}

Glutamine is an amino acid that is a favored food of the GI tract. It is necessary for cell mitosis. Topical and systemic glutamine preparations have been studied for mucositis with inconsistent results. A randomized double-blind, placebo controlled trial by Pytlik et al\textsuperscript{231} reported that in BMT patients who received intravenous alanyl-glutamine dipeptide the incidence of severe oral mucositis was higher. A single Phase III trial of Saforis (L-glutamine in a proprietary oral drug-delivery system) by Peterson et al\textsuperscript{232} showed a reduction in oral mucositis among patients who were receiving anthracycline-based chemotherapy.
The FDA issued an approvable letter in October 2006 for “oral mucositis” and asked for an additional phase III trial before full approval evaluation. There are currently no published HN RT data to support the use of this agent.

**Other Agents**

**Allopurinol**

Nakamura et al\(^{233}\) reported that Allopurinol may theoretically be expected to prevent 5-FU–associated stomatitis by means of both direct and indirect actions to oral mucosa, which include inhibitory actions on xanthine oxidase, superoxide dismutase, orotidylate decarboxylase, as well as proteases. Few studies by Clark et al\(^{234}\) and Tsavaris et al\(^{235}\) reported promising results of a protective effect from an allopurinol mouthwash in 5-FU–induced mucositis. But two controlled trials by Loprinzi et al\(^{236}\) and Porta et al\(^{237}\) did not confirm the same results. A randomized double blind study by Duenas-Gonzalez et al\(^{238}\) demonstrated that prophylaxis use of oral misoprostol during high-dose chemotherapy did not reduce the incidence of severe oral mucositis.

**Pentoxifylline**

An animal study by Lima et al\(^{239}\) showed beneficial effects of pentoxifylline and thalidomide on 5FU induced mucositis in hamster model. A phase I-II trial by Bianco et al\(^{240}\) reported beneficial effects of pentoxifylline in reducing transplant related oral mucositis in BMT patients. But further well controlled randomized trials by Attal et al\(^{241}\) and Clift et al\(^{242}\) showed no promising results in reducing treatment related oral mucositis in BMT patients. Another well controlled cross over trial by Verdi et al,\(^{243}\) also reported that pentoxifylline was ineffective for preventing mucositis in patients receiving cisplatin and 5-FU. A study by Rothwell et al\(^{244}\) assessed topical corticosteroids for radiation induced mucositis in a small number of patients.
Other Modalities used for the treatment of Oral Mucositis:

Chinese herbs, honey, aloe-vera, indigo wood root, histamine gel etc has been used to prevent and treat cancer treatment induced oral mucositis.\textsuperscript{15}

Review Studies

Palifermin

A recent review by Barasch, Epstein and Tilashalski\textsuperscript{245} concluded that KGF reduces the incidence, duration and severity of mucosal lesions in the oral cavity. However, whether or not this effect translates into a similarly reduced incidence of infection, febrile neutropenia and improved nutrition and survival is not clear. Similarly, the GVHD benefits observed in animal models are not apparent in human studies. Another review by Rzepecki et al\textsuperscript{246} also concluded the same results.

Overall Modalities

A very recent Cochrane database review study by Worthington et al\textsuperscript{15} concluded that ten interventions were found to have some benefit for preventing or reducing the severity of cancer treatment induced mucositis. Two interventions, cryotherapy (ice chips) and KGF (palifermin\textsuperscript{®}) showed some benefit in preventing mucositis. Sucralfate is effective in reducing the severity of mucositis, and a further seven interventions, aloe-vera, amifostine, intravenous glutamine, granulocyte-colony stimulating factor (G-CSF), honey, laser and antibiotic lozenges containing polymixin/tobramycin/amphotericin (PTA) showed weaker evidence of benefit. These were evaluated in patients with different types of cancer, undergoing different types of cancer treatment. Authors reported that benefit may be restricted to the disease and treatment combinations evaluated. They also suggested that there is a need for further well designed trials
with sufficient numbers of participants to perform subgroup analyses by type of disease and chemotherapeutic agent.

**2B.4 ECONOMIC IMPACT**

Treatment of mucositis and its associated morbidities can cause a significant economic burden on cancer patients. Patients may incur increased costs for treatment, including in some cases hospitalization or emergency room visits for complications or life-threatening situations. A retrospective analysis study by Elting et al\(^{247}\) of patients who received myelo-suppressive therapy with or without radiation therapy, the average cost for treating patients without oral mucositis was $3,893, whereas this almost doubled $6,618 with grade 1/2 oral mucositis and rose to $9,458 in those with grade 3/4 toxicity. Another review by Trotti et al\(^{14}\) reported that, the overall incidence of mucositis-related hospitalization was 16\% in three studies involving a total of 700 patients; the rate was highest in patients receiving altered fraction radiation therapy (32\%). One study by Peterman et al\(^{248}\) estimated that the mean cost of treatment-related mucositis in patients with HNC ranged from $2,949 to $4,037 per treatment, results were similar as estimated by Elting et al.\(^{247}\)

A study by Sonis et al\(^{249}\) of 92 patients undergoing hematopoietic stem cell transplant, reported that myelo-suppressive or myelo-ablative therapy induced severe mucositis lengthened the hospitalization by an average of 2.6 days, increase the duration on total parenteral nutrition and use of opioid analgesics, and added $25,405 to the mean hospitalization cost compared with those without mucositis. They also reported that total hospitalization costs increased as a function of severity of oral mucositis, as did the 100-day mortality rate. Similarly, Elting et al\(^{247}\) reported that the mean length of hospitalization was 4 days, 6 days, and 12 days during cycles with no mucositis, oral mucositis, and GI mucositis, respectively.
In addition oral mucositis may result in increased use of antibiotics and can cause dose reductions and/or delays in chemotherapy or radiotherapy. Overall evidence suggests that severe mucositis is associated with increased healthcare utilization, significantly greater hospitalization and treatment costs, and higher mortality. Hence it poses significant additional burden on patients receiving cancer treatment.

2B.5 QUALITY OF LIFE

Historically primary outcomes for the success of any anticancer intervention were mainly reported by objective tumor response, overall survival and/or disease free survival. Since last three decades, with the therapeutic advancements (e.g. multimodalities regimen) resulted in increasing number of cancer survivors, hence more focus has been added in addition to the above parameters is how to improve their quality of life (QOL). The loss of health and/or the consequences of treatment can result in physical or functional impairment, disruption of social and family interactions, and psychological distress, all of which can affect QOL. As a result, health care interventions must be judged not only by their impact on survival, but also on QOL. Extending survival does not always correlate with improvements in QOL, and conversely, specific treatments may not necessarily prolong life but may enhance its quality. Understanding the patient's perception of his/her disease and its treatment is critical to comprehensive cancer care. For HNC patients, appreciation of the full impact of the disease and its treatment is critical. Since the majority of these patients are diagnosed with advanced stage disease, treatment tends to be aggressive, with significant acute and long-term effects. Both the disease and the consequences of therapy interfere with basic human functions, including eating, speaking and breathing.
Health-related QOL is a subjective, multi-attribute construct defined by the WHO as follows: “an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, standards and concerns. It is a broad ranging concept affected in a complex way by the person’s physical health, psychosocial state, level of independence, social relationships, and their relationships to salient features of their environment.”

“Health-related QOL refers to the patient's perception of the impact of illness before, during, and after treatment. There are two fundamental premises of health-related QOL: 1) Multi-dimensionality (QOL encompasses a broad range of domains) and 2) Subjectivity (two people may have substantially different reactions to a similar disability)

These two elements distinguish QOL assessment from standard toxicity ratings or global functional ratings (e.g. the Karnofsky scale of performance status). Both of these are assessed by the health care provider rather than the patient and summarize only one area (i.e., somatic symptoms or performance) rather than multiple domains. QOL differs from other traditional treatment endpoints such as response rate or survival in that it changes over time. As a result, the general strategy of QOL evaluation is to examine these changes over the course of the disease and its treatment. While specific definitions may vary by investigator, QOL is generally considered to include at least three and often four dimensions:

1. Physical/somatic (e.g., pain, nausea, and fatigue)
2. Functional (e.g., energy level and activities of daily living)
3. Social (e.g., maintenance of relationships with family and friends)
4. Psychological/emotional (e.g., mood, anxiety, and depression)
Assessment of QOL

Generally, QOL measures can be categorized as generic measures or specific measures.

Generic measures:
These are applicable across diseases, many well developed and validated generic measures are available and include

Medical Outcomes Study 36-Item Short-Form Survey (SF-36)
General Health Questionnaire (GHQ)-20
Rotterdam Symptom Checklist, Functional Living Index

Specific measures
These are disease, site and/or treatment modality-specific measures, many well developed and validated measures specific to cancer are available and include

Functional Assessment of Cancer Therapy - General (FACT-G)
European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire 30 (EORTC QLQ-C30)

It is important to note that these various instruments are not interchangeable; although they all measure some aspect of QOL, they provide different information.

Measures specific to HNC:
There are a number of frequently employed reliable and validated HNC specific instruments:

FACT Head and Neck (FACT-H&N)
FACT Head and Neck Symptom Index (FHNSI)
European Organization for Research and Treatment of Cancer QOL Questionnaire - Head and Neck Specific Module (EORTC QLQ)-H&N35
University of Washington Quality of Life (UW-QOL)
Head and Neck Radiotherapy Questionnaire (HNRQ)
University of Michigan Head and Neck Quality of Life Questionnaire (HNQOLQ)
Quality of Life Radiation Therapy Instrument (QOL-RTI)
M. D. Anderson Dysphagia Inventory (MDADI)
Voice-related Quality of Life Measure (V-RQOL)
Performance Status Scale for Head and Neck Cancer (PSS-HN)

The Functional Assessment of Cancer Therapy-Head and Neck Cancer

The Functional Assessment of Cancer Therapy - Head and Neck (FACT-H&N) consists of the FACT-G, to which all-item site-specific, HNC subscale is added. The H&N subscale evaluates the unique concerns of patients with HNC (e.g., swallowing, chewing). The FACT-G has 4 subscales: physical well-being (PWB) (7 items), social/family well-being (SWB) (7 items), emotional well-being (EWB) (6 items), and functional well-being (FWB) (7 items). All items have a Likert-type response scale (ranging from 0 [not at all] to 4 [very much]). Item responses on subscale and total scores were calculated as described in the FACT-HN scoring guidelines. Reliability and validity of FACT-HN has been already established in various Indian languages. A study by List et al reported decreased performance status and QOL in patient completing the concurrent chemoradiotherapy.

2B.5a Oral Mucositis and QOL

Almost all patients with head and neck cancer experience oropharyngeal complications during and after chemoradiotherapy. Oral mucositis is a most debilitating acute adverse event associated
with cancer treatment and in HNC patients its incidence as high as 100%. Oral mucositis associated pain causes significant impairment with taste, eating, swallowing, speech and sleeping functions. Oral mucositis may also be associated with excessive oropharyngeal secretions, facial edema and cosmetic embarrassment in some severe cases. Oral mucositis is also associated with the sequelae like feeding tube dependency, weight loss, infections, aspiration and increased hospitalization and treatment cost. These all factors significantly impair the QOL of HNC patients in all spheres including physical, emotional, functional and social domains. Few studies have reported that decreased oral functions following cancer therapy in HNC patients were related to decrease QOL.

2B.5b Patient reported measures of Mucositis

There are two scales Oral Mucositis Daily Questionnaire and Oral Mucositis Weekly Questionnaire- Head Neck which specifically measures patient’s perception of oral mucositis.

**Oral Mucositis Weekly Questionnaire- Head and Neck (OMWQ-HN)**

OMWQ-HN is a patient self-administered questionnaire to assess the effects of mucositis in patients with head and neck cancer. This was developed by Epstein et al. It includes domains and questions related to mucositis symptoms, including mouth and throat soreness and their impact on patient well-being and function.

The OMWQ-HN consists of 12 items that assess patient well-being and function. The time frame for reference is the past week. All questions use a Likert-type response format. The first 2 questions assess global health and quality of life (QOL) and are taken from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; the questions are rated on a 7-point scale, with 1 indicating very poor and 7 indicating excellent: 1) How
would you rate your overall health during the past week? 2) How would you rate your overall QOL during the past week? The third question quantifies mouth and throat soreness (MTS), the patient is experiencing on a 5-point scale, with 0 indicating no soreness and 4 indicating extreme soreness: 3) How much MOUTH AND THROAT SORENESS did you experience in the past week? If the patient marks 0, then he or she is instructed to stop; and, if soreness is >0, then the remaining 4 questions are completed.

The fourth question, which is made up of 6 items, addresses the impact of MTS on patient function and includes a 5-point scale, with 0 indicating not limited and 4 indicating unable to do: 4) How much did MOUTH AND THROAT SORENESS limit you in each of the following activities during the past week: 1) sleeping, 2) swallowing, 3) drinking, 4) eating, 5) talking, 6) brushing your teeth? The remaining 3 questions assess the degree of mouth and throat pain and soreness using an 11-point scale, with 0 indicating no pain or soreness and 10 indicating the worst pain or soreness imaginable or possible: 5) On a scale from 0 to 10, how would you rate your OVERALL MOUTH AND THROAT SORENESS during the past week? 6) On a scale from 0 to 10, what number best describes the MOUTH PAIN that you have experienced in the past week? 7) On a scale from 0 to 10, what number best describes the THROAT PAIN that you have experienced in the past week?

In a prospective multicenter observational study by Epstein et al evaluated the validity, reliability, feasibility of this 12 item OMWQ-HN questionnaire for internal and test retest consistency, compliance with the program, and against the FACT-HN, which served as a benchmark tool for validity measurements.  

Preliminary results of this study suggested that OMWQ-HN is a promising, useful tool to evaluate mucositis in patients undergoing treatment for HNC. Responses to test items were
internally consistent, and test-retest coefficients were acceptable. Ninety percent of the patients completed the 6 week study, suggesting that the intervention was feasible. Also the comparison between the OMWQ-HN and FACT-HN suggested that the OMWQ-HN detected the symptomatic conditions accurately and was as sensitive as the FACT-HN at detecting changing conditions over time. In the end authors concluded that OMWQ-HN is a reliable supportive tool in the care of HNC patients as well as a useful research tool. A prospective study by Murphy et al the OMWQ-HN was administered to HNC patients to evaluate morbidity while resource utilization data associated with mucositis was collected concurrently. 75 HNC patients receiving chemo- and/or radiation therapy completed the OMWQ-HN weekly over the period of six weeks. By week six, 60% of patients were experiencing significant toxicities related to swallowing, and 76% of patients reported grade 3 or 4 mouth and throat soreness.
CHAPTER IIC

LOW LEVEL LASER THERAPY-
AN OVERVIEW

This chapter explains about the Low level laser therapy which includes its brief history, components, mechanism of production, properties, parameters, mechanisms of action on cells, and evidence of effectiveness in various conditions. Also some of the contraindications of Low level laser therapy have been reported at the end of this chapter.
2C.1 HISTORICAL BACKGROUND

Phototherapy means the treatment of various health related conditions with the help of light. Phototherapy may be in form of exposure to daylight or to specific wavelengths of light using lasers, light emitting diodes, fluorescent lamps and very bright full spectrum light etc. with the use of various instruments. The light is administered for a prescribed amount of time and, in some cases, at a specific time of day. People of many ancient civilizations like Ancient Greece, Egypt, and Rome practiced various forms of phototherapy. The Inca, Assyrian and early German settlers also worshipped the sun as a health bringing deity. Indian medical literature dating to 1500 BC describes a treatment combining herbs with natural sunlight to treat non-pigmented skin areas. Buddhist literature from about 200 AD and 10th-century Chinese documents also made similar references.

Niels Finsen (Faroese physician) is believed to be the father of modern phototherapy. He developed the first artificial light source for this purpose, and used his invention to treat lupus vulgaris. He received the Nobel Prize in Physiology or Medicine in 1903. Since then, a large array of treatments has been developed from the use of controlled light.261

In 1916, Albert Einstein conceived the theory of Light Amplification through Stimulated Emission of Radiation or LASER. Low Level Laser Therapy (LLLT) is a form of phototherapy where Lasers having low intensity (1mW-500mW) are used for the treatment of various medical conditions including pain relief, reduce inflammation, and promote tissue regeneration. The Low level laser has a typical narrow spectral width in the red or near infrared (NIR) spectrum (600nm-1000nm), with a power density (irradiance) between 1mw-5W/cm². It is applied over the treatment area for a minute or so, a few times a week for several weeks.262
Unlike other medical laser procedures, LLLT does not have an ablative or thermal mechanism, but rather it has a photochemical effect comparable to photosynthesis in plants whereby the light is absorbed and exerts a chemical change. The phenomenon was first published by Professor Endre Mester at Semmelweis University; Budapest, Hungary in 1967 a few years after the first working laser was invented. Dr. Mester is recognized by many as the grandfather of laser therapy. Dr. Mester conducted an experiment to test if laser radiation might cause cancer in mice. He shaved the hair off their backs, divided them into two groups and irradiated one group with a low powered ruby laser (694-nm). The laser irradiated group did not get cancer and to his surprise, the hair grew back more quickly than the non-irradiated group. He called this phenomenon “Laser Biostimulation”. Dr. Mester and his colleagues reported various studies about improvement in wound healing, muscle fiber regeneration with the application of a low-energy (1 J/cm²) ruby laser.

LLLT has been investigated and used clinically for over 40 years, mostly in Eastern Europe and Asia and over 20 years in US. The worldwide interest in LLLT is illustrated by its use in more than 85 institutions in over 37 countries. Since the first study was reported in 1967, more than 3000 papers have been published in a range of journals worldwide and the value of LLLT is much better reported than many believe. Its scientific background is sound enough to say that it is both safe and effective.
2C.2 COMPONENTS OF LASER

Laser system has three essential components

1.) A lasing medium

2.) An energy source

3.) Mechanical structure of the laser

Low level lasers lies in the near to far infra-red range of the electromagnetic spectra (visible red to visible red). *(Figure K)*

*Figure K: Principal components of LASER [1=Active laser medium, 2=Laser pumping energy (Energy Source), 3=High reflector, 4=Output coupler, 5=Laser beam]*

2C.2a Lasing medium

The lasing medium is a material which is capable of being excited by an outside source and absorbing that energy produced when electrons are excited from one level to another. Lasing media can be gaseous, liquid, solid crystal or semiconductor in nature. Helium-neon is an example of a gas medium laser while gallium aluminum arsenide is an example of a semiconductor medium laser. The selection of the lasing medium is important since this will
dictate the wavelength of the device’s output and ultimately determine the color of the beam and depth of penetration.

Various lasing medium have been used to create the lasers used for LLLT. Initial research used lasers based on inert gases, including helium neon (HeNe; 632.8nm), ruby (694 nm), argon (488 and 514 nm), and krypton (521, 530, 568, and 647 nm). Subsequent studies have used semiconductor laser diodes, including gallium arsenide (GaAs; 904 nm) and gallium aluminum arsenide (GaAlAs; 820 and 830 nm) devices. Most LLLT research studies, perhaps owing to cost and availability issues, have used HeNe lasers, but many newer studies are preferentially employing the newer GaAs lasers.

**Figure L: Helium Neon LASER**

**2C.2b Energy Source**

The energy source most common to systems used to treat various inflammatory conditions will be electrical power. Lasers operating in the 632 (visible red) to 1000nm (far infrared) wavelength and used to treat oral mucositis or its associated pain are typically driven by a local main power supply.
2C.2c Mechanical structure of the laser

Early therapeutic lasers utilized two wavelength specific mirrors mounted parallel to each other and a fixed distance from each other (a multiple of the lasers wavelength) so as to reflect only a certain wavelength range. This mechanical structure holds true today for many lasers except those using semiconductor technology. These units use polished diodes and special lenses to both selectively emit and concentrate the laser beam consisting of light particles or photons. (Figure M)

Figure M: Schematic diagram of Semiconductor Laser
2C.3 MECHANISM OF HELIUM NEON LOW LEVEL LASER PRODUCTION

A Helium Neon laser usually is a type of small gas laser, the process of its production initiates with the collision of electrons from the electrical discharge with the Helium atoms in the gas. This excites Helium atoms from their ground state to the $2^3S_1$ and $2^1S_0$ long lived, metastable excited states. The collision of these excited Helium atoms with the ground state Neon atoms results in transfer of energy to the Neon atoms, which excite Neon atoms into 3s2 level this is due to a coincidence of energy levels between the helium and neon atoms. The mechanism of production of low level helium neon laser 632.8nm has been described in the figures given below. *(Figure N)*

*Figure N: Mechanism of Helium-Neon Laser production*
2C.4 PROPERTIES OF LASER

Distinguishing features of Laser light from other forms of light is that it is monochromatic, directional and coherent.

Mono-chromaticity:

Laser always have single specific wavelength and defined frequency and hence for a defined wavelength there is a defined color. The spectral emission (bandwidth) from a laser is much more limited than other sources of light such as incandescent or fluorescent light. Lasers emit at specific wavelengths such as 632.8nm (helium-neon laser) whereas, by comparison, an infra-red lamp emits many wavelengths within the infra-red spectral range (multiple wavelengths). This becomes important as wavelength becomes the primary determinant of depth of penetration.

Collimation:

The term collimation refers to a laser’s high degree of beam parallelity and is the opposite of beam divergence. This becomes clinically important since the greater the divergence, the larger the spot size for treatment and the lower the power density. A more focused beam increases the ocular hazard for both operator and patient. To minimize losses in power, the laser should be kept as close to the target tissue as possible. It is important to note that non-laser sources of light scatter light at many wavelengths in different directions, in stark contrast to laser light which is focused almost perfectly parallel and in one direction.

Coherence:

Finally, a laser is said to have coherence, a property whose biological significance has been debated by researchers. Coherence suggests a synchronicity in light waves so that each wave maintains a precise spatial relationship with other waves and that this pattern is maintained over long distances.\textsuperscript{22,265}
2C.5 PARAMETERS OF LOW LEVEL LASER THERAPY

Low level laser as a treatment modality can be described in two types of parameters i.e. Irradiation parameters and a “dose” (the irradiation time).

**Irradiation Parameters**

**Power:** Power is the primary defining factor and is measured in Watts. Power used for LLLT lies within a range of $10^{-3}$ to $10^1$ W.

**Wavelength:** Light is electromagnetic energy which travels in discrete packets that also having a wave-like property. Wavelength is measure in nanometers (nm) and is visible in the 400-700 nm range. A wavelength between 300 and 10,600 nm has been used in various LLLT studies.

**Irradiance:** Often called Intensity, or Power Density and is calculated as

\[
\text{Irradiance} = \frac{\text{Power (W)}}{\text{Area (cm}^2\text{)}}
\]

Power density of $10^{-2}$ to $10^0$ W/cm$^2$ has been used in various LLLT studies.

**Pulse structure:** If the beam is pulsed then the Power should be the Average Power and calculated as follows:

\[
\text{Average Power (W)} = \text{Peak Power (W)} \times \text{pulse width (s)} \times \text{pulse frequency (Hz)}
\]

A pulse rate of 0 (continuous) to 5,000 Hz, pulse duration of 1 to 500 milliseconds, an inter-pulse interval of 1 to 500 milliseconds has been used in various LLLT studies.

**Coherence:** Coherent light produces laser speckle, which has been postulated to play a role in the photo-biomodulation interaction with cells and sub-cellular organelles. Coherence length depends on spectral bandwidth.
**Polarization**: Polarized light may have different effects than otherwise identical non-polarized light (or even 90-degree rotated polarized light). However, it is known that polarized light is rapidly scrambled in highly scattering media such as tissue (probably in the first few hundred µm). Polarization can be Linear or circular.

**Dose**

Dose delivered to the tissues is calculated by the formula:

\[
\text{Dose} = \text{Power (W)} \times \frac{\text{irradiation time(s)}}{\text{area irradiated(cm}^2)}
\]

LLLT Doses delivered to treatment areas described in various studies ranges from \(10^{-2}\) to \(10^2\) J/cm\(^2\).

Energy (J) or energy density (J/cm\(^2\)) is often used as an important descriptor of LLLT dose, but this neglects the fact that energy has two components, power and time,

\[
\text{Energy (J)} = \text{Power (W)} \times \text{Time (s)}
\]

and it has been demonstrated that there is not necessarily reciprocity between them; in other words, if the power doubled and the time is halved then the same energy is delivered but a different biological response is often observed.
Energy (Joules): Calculated as:

\[ \text{Energy (J)} = \text{Power (W)} \times \text{time (s)} \]

Using Joules as an expression of dose is potentially unreliable as it assumes reciprocity (the inverse relationship between power and time).

Energy Density (J/cm²): Common expression of LLLT “dose” is Energy Density. This expression of dose again is potentially unreliable as it assumes a reciprocity relationship between irradiance and time.

Irradiation Time (seconds): The safest way to record and prescribe LLLT is to define all the irradiation parameters and then define the irradiation time as “dose”. A total irradiation time in various LLLT studies has been varied from 10 to 3,000 seconds.

Treatment interval: The effects of different treatment interval are underexplored at this time though there is sufficient evidence to suggest that this is an important parameter.\textsuperscript{21,22,265-269}
2C.6 MECHANISMS OF LOW LEVEL LASER THERAPY

2C.6a Cellular Chromophores and First Law of Photobiology

The first law of photobiology states that for low power visible light to have any effect on a living biological system, the photons must be absorbed by electronic absorption bands belonging to some molecular photo-acceptors, or chromophores. A chromophore is nothing but a molecule (or part of a molecule) which gives some particular color to the compound of which it is an ingredient. Chromophores almost always occur in one of two forms: conjugated pi electron systems and metal complexes. Examples of such chromophores are chlorophyll (used by plants for photosynthesis), hemoglobin, cytochrome c oxidase (Cox), myoglobin, flavins, flavoproteins and porphyrins. Figure P illustrates the general concept of LLLT.

Figure P: Schematic diagram showing the absorption of red and near infrared light by specific cellular chromophores or photo-acceptors localized in the mitochondrial respiratory chain.


2C.6b Action Spectrum and Tissue Optics

Tissues have some optical properties and there is a so-called “optical window” in tissue, where the effective tissue penetration of light is maximized. This optical window runs approximately from 650 nm to 1200 nm. (Figure Q)

![Figure Q: Therapeutic window of LASER](image)

![Figure R: Absorption spectra of the main chromophores in living tissue on a log scale showing the optical window where visible and NIR light can penetrate deepest into tissue.](image)
The absorption and scattering of light in tissue are both much higher in the blue region of the spectrum than the red, because the principle tissue chromophores (hemoglobin and melanin) have high absorption bands at shorter wavelengths, tissue scattering of light is higher at shorter wavelengths, and furthermore water strongly absorbs infrared light at wavelengths greater than 1100-nm. Therefore the use of LLLT in animals and patients almost exclusively involves red and near-infrared light (600-1100-nm).\textsuperscript{272}(Figure R)

Phototherapy is characterized by its ability to induce photo-biological processes in cells. Exact action spectra are needed for determination of photo-acceptors as well as for further investigations into cellular mechanisms of phototherapy. The action spectrum shows which specific wavelength of light is most effectively used in a specific chemical reaction.\textsuperscript{273} The fact that defined action spectra can be constructed for various cellular responses confirms the first law of photobiology described above (light absorption by specific molecular chromophores).

\textit{2C.6c Mitochondrial Respiration and ATP}

Current research about the mechanism of LLLT effects inevitably involves mitochondria. Mitochondria play an important role in energy generation and metabolism. Mitochondria are sometimes described as “cellular power plants”, because they convert food molecules into energy in the form of ATP via the process of oxidative phosphorylation. (Figure S)
Figure S: Mitochondrial respiratory chain consisting of contains five complexes of integral membrane proteins: NADH dehydrogenase (Complex I), succinate dehydrogenase (Complex II), cytochrome c reductase (Complex III), cytochrome c oxidase (Complex IV), and ATP synthase (Complex V).

The mechanism of LLLT at the cellular level has been attributed to the absorption of monochromatic visible and Near Infra-Red (NIR) radiation by components of the cellular respiratory chain. Several pieces of evidence suggest that mitochondria are responsible for the cellular response to red visible and NIR light. The effects of He-Ne laser and other illumination on mitochondria isolated from rat liver have included increased proton electrochemical potential, more ATP synthesis, increased RNA and protein synthesis, and increases in oxygen consumption, membrane potential, and enhanced synthesis of NADH and ATP.

2C.6d Cytochrome C Oxidase and Nitric Oxide Release

Absorption spectra obtained for Cytochrome C Oxidase (Cox) in different oxidation states were recorded and found to be very similar to the action spectra for biological responses to
Therefore it was proposed that Cox is the primary photo-acceptor for the red to Near Infra-Red range in mammalian cells. Nitric oxide produced in the mitochondria can inhibit respiration by binding to Cox and competitively displacing oxygen, especially in stressed or hypoxic cells. Increased nitric oxide (NO) concentrations can sometimes be measured in cell culture or in animals after LLLT due to its photo release from the mitochondria and Cox. It has been proposed that LLLT might work by photo-dissociating NO from Cox, thereby reversing the mitochondrial inhibition of respiration due to excessive NO binding. Figure T illustrates the photo-dissociation of NO from its binding sites on the heme iron and copper centers where it competitively inhibits oxygen binding and reduces necessary enzymatic activity, thus allowing an immediate influx of oxygen and resumption of respiration and generation of reactive oxygen species.

Figure T: When NO is released from its binding to heme iron and copper centers in cytochrome c oxidase by the action of light, oxygen is allowed to rebind to these sites and respiration is restored to its former level leading to increased ATP synthesis.


2C.6d NO signaling

In addition to NO being photo-dissociated from Cox as described, it may also be photo-released from other intracellular stores such as nitrosylated hemoglobin and nitrosylated myoglobin.\textsuperscript{280} Light mediated vasodilatation was first described in 1968 by R F Furchgott, in his nitric oxide research that lead to his receipt of a Nobel Prize thirty years later in 1998.\textsuperscript{281} Later studies conducted by other researchers confirmed and extended Furchgott’s early work and demonstrated the ability of light to influence the localized production or release of NO and stimulate vasodilatation through the effect NO on cyclic guanine monophosphate (cGMP). This finding suggested that properly designed illumination devices may be effective, noninvasive therapeutic agents for patients who would benefit from increased localized NO availability.

2C.6e Reactive oxygen species and gene transcription

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are involved in the signaling pathways from mitochondria to nuclei. Reactive oxygen species (ROS) are very small molecules that include oxygen ions such as superoxide, free radicals such as hydroxyl radical, and hydrogen peroxide, and organic peroxides. They are highly with biological molecules such as proteins, nucleic acids and unsaturated lipids. ROS form as a natural by-product of the normal metabolism of oxygen and have important roles in cell signaling,\textsuperscript{282} regulating nucleic acid synthesis, protein synthesis, enzyme activation and cell cycle progression.\textsuperscript{283} LLLT was reported to produce a shift in overall cell redox potential in the direction of greater oxidation\textsuperscript{16} and increased ROS generation and cell redox activity have been demonstrated.\textsuperscript{284-290} These cytosolic responses may in turn induce transcriptional changes. Several transcription factors are regulated by changes in cellular redox state. But the most important one is nuclear factor β (NF-β) activated
after LLLT and is instrumental in causing transcription of protective and stimulatory gene products. (**Figure U**)

**Figure U**: Reactive oxygen species (ROS) formed as a result of LLLT effects in mitochondria may activate the redox-sensitive transcription factor NF-κB (relA-p50) via protein kinase D (PKD).

**2C.6f Downstream cellular response**

Although the underlying mechanism of LLLT are still not completely understood, in vitro studies, animal experiments and clinical studies have all tended to indicate that LLLT delivered at low doses may produce a better result when compared to the same light delivered at high doses. LLLT can prevent cell apoptosis and improve cell proliferation; migration and adhesion at low levels of red/NIR light illumination. (**Figure V**)
Figure V: The downstream cellular effects of LLLT signaling include increases in cell proliferation, migration and adhesion molecules. Cell survival is increased and cell death reduced by expression of proteins that inhibit apoptosis.

LLLT at low doses has been shown to enhance cell proliferation in vitro in several types of cells: fibroblasts, keratinocytes, endothelial cells, and lymphocytes. The mechanism of proliferation was proposed to involve photo-stimulatory effects in mitochondria processes, which enhanced growth factor release, and ultimately led to cell proliferation. Kreisler et al. showed that the attachment and proliferation of human gingival fibroblasts were enhanced by LLLT in a dose-dependent manner. LLLT modulated matrix metalloproteinase activity and gene expression in porcine aortic smooth muscle cells. Shefer et al. showed that LLLT could activate skeletal muscle satellite cells, enhancing their proliferation, inhibiting differentiation and regulating protein synthesis.

2C.6g Downstream tissue response
There have been several animal model and clinical studies that demonstrated highly beneficial LLLT effects on a variety of diseases, injuries, and has been widely used in both chronic and acute conditions. \(\text{Figure W}\) LLLT may enhance neo-vascularization, promote angiogenesis and increase collagen synthesis to promote healing of acute\(^{301}\) and chronic wounds.\(^{302}\) LLLT provided acceleration of cutaneous wound healing in rats with a biphasic dose response favoring lower doses.\(^{303}\) LLLT can also stimulate healing of deeper structures such as nerves,\(^{304}\) tendons,\(^{305}\) cartilage,\(^{306}\) bones,\(^{307}\) and even internal organs.\(^{308}\) LLLT can reduce pain,\(^{309}\) inflammation,\(^{310}\) and swelling\(^{311}\) caused by injuries, degenerative diseases or autoimmune diseases. Oron reported beneficial effect of LLLT on repair processes after injury or ischemia in skeletal and heart muscles in multiple animal models in vivo.\(^{312-315}\) LLLT has been used to mitigate damage after strokes (in both animals\(^{316}\) and humans\(^{317}\)), after traumatic brain injury\(^{318}\) and after spinal cord injury.\(^{319}\)

\(\text{Figure W}:\) Beneficial tissue effects of LLLT can include almost all the tissues and organs of the body.
2C.7 Evidence for effectiveness of LLLT

Since 1967 over 100 phase III, randomized, double-blind, placebo-controlled, clinical trials (RCTs) have been published and supported by over 1,000 laboratory studies investigating the primary mechanisms and the cascade of secondary effects that contribute to a range of local tissue and systemic effects. RCTs with positive outcomes have been published on pathologies as diverse as osteoarthritis, tendonopathies, wounds, back pain, neck pain, muscle fatigue, peripheral nerve injuries, and strokes, nevertheless results have not always been positive. This failure in certain circumstances can be attributed to several factors including dosimetry (inadequate or too much energy delivered, inadequate or too much irradiance, inappropriate pulse structure, irradiation of insufficient area of the pathology), inappropriate anatomical treatment location and concurrent patient medication (such as steroidal and non-steroidal anti-inflammatory drugs which can inhibit healing).

2C.8 Contraindications of LLLT

Till now none of the literature reported any adverse event associated with LLLT. As low level laser devices come under class III medical devices which are considered as non-significant risk medical devices. The risk of eye injury is minimal but must be considered this can be avoided by wearing wavelength specific protective eye goggles by the therapist as well as patients.

1. Application over eyes due to risks of retinal damage.
2. Cancerous growths due to risk of increase activity of cancer cells.
3. Pregnancy – over & around uterus due to increased risk of interference with fetal growth.
4. Over cardiac region and Vagus nerve due to risk of altered activity of pacemaker cells.
5. Growth plates in children may alter normal cell growth.
6. Over and around thyroid gland & endocrine glands can alter their activities.
CHAPTER II D

LOW LEVEL LASER THERAPY FOR ORAL MUCOSITIS- AN UPDATED REVIEW

This chapter gives an insight of various studies including case reports, non-randomized and randomized trials done using low level laser therapy for the prevention and treatment of oral mucositis caused by various cancer therapies till March 2012.
2D.1 Low Level Laser Therapy for Oral Mucositis- An Updated Review

LLLT as a preventive and curative modality for oral mucositis has been used over last 20 years when first report of its use for chemotherapy (5FU) induced oral mucositis by Ciais et al appeared in 1992 in Bulletin cancer. Recent years there is sudden rise in research studies to prove the efficacy of LLLT for the prevention and treatment of oral mucositis. Most of research in human subjects involved the patients receiving therapy for HSCT. This review has involved all kind of human studies including case reports and RCTs and Review articles/Meta-analysis for the prevention and treatment of oral mucositis induced by cancer treatment. The whole review is divided into three parts

2D.1a LLLT FOR CHEMOTHERAPY INDUCED ORAL MUCOSITIS

Ciais et al(1992), did a preliminary non-randomized study using helium-neon laser therapy on mucositis in cancer patients receiving combination chemotherapy including 5-fluorouracil, reported that Curative laser therapy reduced the time to repair of mucositis lesions and the rate of therapeutic modifications. Oral mucositis was observed during 43% of 53 chemotherapy cycles in the retrospective control population while the incidence of oral complications was reduced to 6% during 101 cycles of chemotherapy. They also reported that all of these patients, even those who have encountered mucositis before receiving preventive laser therapy, terminated their cancer therapy as originally scheduled.

Pourreau et al (1992), another preliminary report in same year showed beneficial effects of LLLT on chemotherapy induced mucositis in cancer patients receiving 5FU.

Kim et al (2001) evaluated the effects of the He-Ne laser(λ=632.8nm, P= 60mW, 400# 600 Hz scanning for 5# 20 minutes) and the Ga-Al-As laser(λ=904nm,P= 40mW) for 30 seconds per point for 5 days per week on oral mucositis caused by anticancer chemotherapy in pediatric
patients (n=9). The result analysis concluded that He-Ne laser and Ga-Al-As (IR) laser treatment reduced the severity and duration of chemotherapy-induced oral mucositis in pediatric oncologic patients. *This was a non-randomized trial and no control group.*

**Wong and Smith (2002),** A pilot study of 15 patients with prior episode of 5-FU induced severe mucositis (grade 3 and 4) were treated with LLLT (λ=830nm, P=70mW, t=15-30min, total dose=50-60J, energy density= 0.7-0.8J/cm²) 24 hours before the chemotherapy and weekly throughout the duration of chemotherapy at the same dose until the mucositis resolved or the chemotherapy cycle was completed. They assessed the intra-oral perfusion using laser Doppler technology and also evaluated the ease and feasibility of the LLLT and the impact of LLLT on improving the patient's quality of life. Results of this study reported that out 15 patients, 3 experienced grade 1 to 2 while one experienced grade 3 to 4 mucositis in remaining 11 patients no mucositis was reported. Pain scores did not increase from the baseline and remains same till the completion of chemotherapy cycle. LLLT was very well tolerated and no discomfort was reported by patients. They did not observe any significant changes in oral perfusion.

**Genot et al (2008)** conducted two clinical trials testing the LLLT: First trial as a secondary prevention in patients (n=26) receiving chemotherapy for various solid tumors that had prior episode of identical chemotherapy induced severe mucositis and reported that success rate was 81% (95%CI = 61-93%). While, second was a randomized controlled study as a curative treatment in patients (n=36) with hematological tumors who already developed chemotherapy induced low-grade oral mucositis and reported that success rate with LLLT was 83% (95%CI = 59-96%), than sham-treated patients (11%; 95%CI = 1-35%). They also reported delayed time of onset of mucositis with LLLT than sham therapy.
Abramoff et al (2008)\textsuperscript{341} A pilot clinical study involving young patients undergoing chemotherapy (22 cycles) were randomized into 2 groups one receiving prophylactic laser-irradiation (group 1), and other receiving placebo light (group 2). Patients who had already presented with mucositis were placed in a group receiving irradiation for therapeutic purposes (group 3, with 10 cycles of CT). Serum granulocyte levels were taken and compared to the progression of mucositis. In group 1, 73\% and 2, 27\% had no incidence of OM. In group 3, the patients had marked pain relief, and a decrease in the severity of OM, even when they had severe granulocytopenia.

In contrast to all the previously mentioned studies a single blinded RCT by Cruz et al (2007)\textsuperscript{342} involving 60 children and adolescent oncology patients undergoing chemotherapy or HSCT reported a totally reverse results where incidence of all the grades of OM was higher in laser than placebo group patients on day 8 and 15 following CT. Though from the various clinical reports showing beneficial effects of LLLT in CT induced OM in cancer patients still there is controversy exists by seeing the results of study by Cruz et al. Hence, very well controlled studies are required to find out therapeutic effects of LLLT in CT induced OM.

2D.1b LLLT FOR ORAL MUCOSITIS IN HEAD AND NECK CANCER PATIENTS

Bensadoun et al (1999),\textsuperscript{30} A multicenter, randomized, double blind, phase III study involving 30 HNC patients receiving only radiation therapy, patients in LLLT (HeNe, $\lambda=632$, $P=60$ mW, spot size=1.2mm, $t=33$s per point, average energy density=2 J/cm$^2$) group (n=15) received prophylactic LLLT at 9 points in the oral cavity in while placebo group (n=15) patients received simple Red light. WHO scale was used to assess the mucositis severity and VAS for pain. Results of this study reported that the incidence of Grade 3 mucositis was 7.6\% in LLLT and
35.2% in placebo group ($P<0.01$). Overall results showed slower progression of mucositis grades in LLLT than placebo group. Also the incidence of severe pain (grade 3) in LLLT and placebo group was 1.9% and 23.8% respectively ($P<0.05$). Pain was significantly reduced throughout the treatment period in LLLT group. In addition, swallowing difficulty was improved in LLLT than placebo group with a median of $4.9\pm1.33$ and $6\pm0.84$ weeks respectively ($p=0.001$). no significant difference between the two groups for the incidence and duration of RT breaks. Patients were stopped for taking analgesics 2 days before assessment of pain scores which is not ethically right.

**Kuhn et al(2005),** Conducted a pilot trial with LLLT (GaAlAs/InGaAlPlaser) in already developed oral mucositis during the course of chemoradiotherapy to decrease the lesions manifestation time and to promote pain control. 15 Patients were divided into 3 groups that received different treatments, 3 times a week for 15 days until the lesions disappeared:

Group A: Laser with 830 nm wavelength, infrared, power 70 mW, and dose 5J/cm$^2$.

Group B: Laser with 685 nm wavelength, visible red, power 35 mW, and dose 5J/cm$^2$.

Group C: Placebo application. Only the hand-piece was used, the laser was not turned on.

The result analysis showed that the infrared laser 830 nm (Group A) was therapeutically superior when compared with the red laser 685 nm (Group B) and the Group C (placebo) in decreasing the severity and duration of mucositis and its associated pain. Group B showed intermediate results between groups A and C. **Study population was not defined as well as no randomization was described.**

**Maiya et al (2006),** A Randomized, controlled Study 50 patients receiving Radiotherapy for head and neck cancer (oral cavity carcinoma) were randomized using computerized program into LLLT (25) and Control (25) groups. LLLT group patients were treated with He-Ne laser
(wavelength 632.8 nm and output of 10mW) and control group patients were given oral analgesics, local application of anaesthetics, 0.9 per cent saline and povidine wash during the course of radiotherapy. At the end of radiotherapy (after 6 wk) mean pain score [2.6±0.64 vs 6.68±1.44] and mucositis grade [1.72± 0.67 vs 3.32±0.69] were significantly lower ($P<0.001$) in the LLLT group compared to control. None of the LLLT group developed grade 3/4 mucositis while all patients in control group developed severe grade mucositis. No blinding was done.

**Kuhn et al(2007),[^344]** A Randomized, Placebo-controlled Study 34 patients receiving Chemotherapy and/or Chemoradiotherapy for cancer (22 HNC+ 12 Lymphomas and Leukemia) were randomized into LLLT(18) and Placebo(16) groups, LLLT group patients were prophylactically treated with a GaAlAs Laser with a continuous 830-nm wavelength, 100 mW power, dose 4 J/cm² for the prevention and treatment of Oral Mucositis. Once OM was diagnosed, the patients had daily OM grading assessments (Common Toxicity Criteria Scale of the National Cancer Institute) before laser or placebo application, and thereafter until complete healing of lesions. Result analysis of the study showed that chemotherapy patients had an OM duration of 5.5 ± 1.2 and 9.3±2.0 in the laser and placebo groups, respectively ($p < 0.001$), with an effect size of 3.8 days. Chemo-radiotherapy patients had an OM duration of 9.5 ± 1.0 and 15.1 ± 1.9 between the laser and placebo groups ($p < 0.001$), with an effect size of 5.6 days. On day 7 after OM diagnosis, 32% of patients presented OM in the laser group and 94% of patients in the placebo group ($p = 0.001$). In the laser group, the mean of OM duration was 6.8 ± 2.2 days, and in the placebo group 11.5 ± 3.5 days ($p < 0.001$). Method of randomization not described.

**Kuhn et al(2008),[^345]** A Randomized, Placebo-controlled Study 23 patients receiving only Radiotherapy for head and neck cancer were randomized into LLLT(11) and Placebo(12) groups, LLLT group patients were prophylactically treated with a GaAlAs Laser with a
continuous 830-nm wavelength, 100 mW power, dose 4 J/cm² for the prevention and treatment of Oral Mucositis. Patients were evaluated for OM (WHO Scale) and pain (VAS) every day. During the 6 weeks of radiotherapy, the mean grade of OM in LLLT group was significantly lower (p < 0.002) than the mean grade in the placebo group. The pain score after each laser or placebo application was significantly lower (p < 0.006) in the LLLT group during the same period. Method of randomization not described.

**Honey Arora et al (2008),** 29 A Randomized, controlled Study 24 patients receiving only Radiotherapy for oral cancer were randomized into LLLT(11) and Control(13) groups, LLLT group patients were treated prophylactically with He-Ne laser (wavelength 632.8 nm and output of 10 mW and energy density = 1.8 J/cm²). The patients were evaluated on each day of treatment for pain severity (NRS), functional impairment (FIS), and oral mucositis (RTOG) and were followed until the end of cancer treatment. This study reported that the overall trend of progression of oral mucositis scores and its associated pain and dysphagia were slower in LLLT group as compare to placebo group. But analgesic use was not significant between the two groups. Results of this study concluded that use of LLLT reduce the severity of oral mucositis, severity of pain, and functional impairment. No randomization was described, no blinding, and small sample size.

**Zanin et al (2009),** 346 72 HNC patients receiving chemo- and radiation therapy were divided into a control group (n=36) and a laser group (n=36) Laser therapy was performed in combination with radiotherapy and chemotherapy twice a week using a diode laser (λ= 660 nm, P=30 mW, spot size = 2 mm, energy = 2 J per point). Results of this study reported that there was no incidence of oral mucositis and its associated pain in laser group while all the patients developed
the mucositis ranging from grade I to III which was associated with pain. This difference was significant from week 1 onwards, increased until 4th week and remained stable up to 7th week. 

*Lima et al (2011),* did a prospective, comparative and non-randomized study involving 25 HNC patients subjected to radio-/chemoradiotherapy. Twelve patients received LLLT (830 nm, 15 mW, 12J/cm²) daily from the 1st day until the end of RT before each sessions during 5 consecutive days, and the other 13 patients received *aluminum hydroxide* 310 mg/5 mL, 4 times/day, also throughout the duration of RT, including weekends. Assessment of OM was done using an oral toxicity scale (OTS) and pain using VAS. In addition QOL was measured using EORTC questionnaires. Results analysis of this study showed that mean OTS and VAS scores were significantly lower in the LLLT group compared to *aluminum hydroxide* group. A significant difference was observed in pain evaluation in the 13th RT session (p=0.036). No interruption of RT was required in both the groups. They concluded that LLLT was more effective in delaying the appearance of severe OM than *aluminum hydroxide.*

*Lino et al (2011),* Use of LLLT on the treatment of oral mucositis in a patient undergoing RT after surgical removal of a squamous cell carcinoma with osseous invasion of the maxilla. Palatal and commissural lesions were treated with LLLT (λ=660 nm, P=40mW, slashed circle=4mm², in contact mode, 5 x 2.4J/cm² per point, 14.4J/cm² per session). For treating the lesion on the patient's nasal mucosa, LLLT (slashed circle=4 mm², λ=780 nm, P=70mW, 3 x 2.1 J/cm² per point, 6.3 J/cm² per session, contact mode) was used on the external area of the nose. A single dose (2.4 J/cm²) with the λ=660 nm laser, as described before, was applied on the entrance of each nostril. LLLT was administered 3times/week for 4 weeks. Treatment results indicate that the use of LLLT on oral mucositis was effective and allowed the patient to carry on the RT without interruption.
Carvalho et al(2011), in a prospective double-blind randomized study involving 70HNC patients were randomized into two LLLT groups: Group1(660nm/15mW/3.8J/cm²/spot size=4mm²) or Group 2 (660nm/5mW/1.3J/cm²/spot size 4mm²) starting on the first day of radiotherapy. Oral mucositis was assessed daily and weekly using the NCI and WHO scales. Oral pain was scored daily with a VAS before laser application. The patients in Group 1 had a mean time of 13.5days (range 6-26days) to present mucositis grade II, while the patients in Group 2 had a mean time of 9.8days (range 4-14days) (both WHO and NCI, P=0.005). In addition, Group 2 also presented a higher mucositis grade than Group 1 with significant differences found in weeks 2 (p=0.019), 3 (p=0.005) and 4 (p=0.003) for WHO scale and weeks 2 (p=0.009) and 4 (p=0.013) for NCI scale. The patients in Group 1 reported lower pain levels (p=0.004). Low-level laser therapy during radiotherapy was found to be effective in controlling the intensity of mucositis and pain. There was no control group involved.

In contrast all these studies reporting positive outcomes with LLLT a recently published RCT by Lima et al(2012), reported that out of 75HNC patients receiving concurrent chemoradiation incidence of severe grades OM was consistently lower in LLLT group(n=37) than placebo group(N=38)but it was not statistically significant. Also they reported the incidence of dysphagia and opioid analgesics use was not significant between the two groups.

Another recently published study by Oton-Leite et al(2012), reported after intraoral LLLT improvement in QOL of HNC patients undergoing radiation/CRT, using University of Washington-QOL questionnaire. Assessment was done at the baseline, at middle and at end of radiotherapy they didn’t take the follow up measures in their study. Also they have not reported the incidence of OM in their study.
2D.1c LLLT FOR CONDITIONING INDUCED ORAL MUCOSITIS HSCT PATIENTS

Barasch et al. (1995) in a double blind prospective controlled study treated 20 patients receiving bone marrow transplantation (BMT) conditioning therapy prophylactically with helium–neon laser irradiation to the oral mucosa either right or left of the midline; the contralateral side was sham treated and served as a control. Patients were treated daily for 5 consecutive days, beginning the day after cessation of chemotherapy. Mucositis severity and pain were scored by the use of OMI-A and B along with ECOG oral toxicity scale and the cumulative scores were analyzed for differences between the laser treated and the sham-treated areas. Result analysis of the study reported that mean scores of VAS ($P = 0.027$) and for each of the OMI scales ($P < 0.005$) were significantly lower for treated than untreated sides when observations were pooled over all examination days. Though ECOG scores were also lower for the treated side, but the results were not statistically significant ($P = 0.171$). The VAS scores for the treated side were statistically significantly lower on day $+9$ ($P = 0.05$), whereas the OMI-A and -B results approached significantly lower levels for the treated side on day $+6$ ($P < 0.053$). Overall they concluded that oral mucositis and pain scores were significantly lower for the treated side, but ulcerative lesions occurred in all patients bilaterally, with progressive increase until day 6 and resolution by day 21. In this study, each patient was his or her own control, which could be of importance, since mucosal damage on the sham-treated side could also have benefited from a distant systemic laser effect.

Cowen et al. (1997), reported a prospective double-blind randomized trial with prophylactic application of low-energy helium–neon laser therapy ($\lambda=632.8\text{nm}$, $P=60\text{mW}$, $ED=1.5\text{J/cm}^2$, $t=10\text{s}/\text{point}$ on 15 points at each anatomic site, total energy delivered at each session=54J) in patients undergoing high dose chemoradiotherapy before autologous bone marrow
transplantation. They randomized 30 consecutive patients to into laser (n=16) and sham treatment (n=14) group. Cross over of patients was done if any patient in sham group developed grade IV mucositis. A daily mucositis index (DMI) and a cumulative oral mucositis score (COMS) were established, and also requirements for narcotics and parenteral nutrition were recorded. Result analysis reported that both the DMI (P=0.04) and the COMS (P<0.05) were significantly reduced among the laser-treated patients. The incidence and duration of grade III mucositis were reduced in laser-treated patients. Moreover, laser application reduced oral pain, as assessed by the patients, and led to a decreased use of morphine. Xerostomia and ability to swallow were improved among the laser-treated patients, but the requirement for parenteral nutrition was not reduced. Overall well designed trial with all outcomes well defined and analyzed. Sample size small is one limitation.

Migliorati et al (2001), treated 11 patients receiving high dose chemotherapy for various hematologic malignancies, ± bone marrow transplantation. The patients received LLLT daily until day 5. Assessment of mucositis (WHO Scale) and pain (VAS) was done. Two patients had mucositis grade I–II, 8 patients had mucositis grade III–IV, and one patient had none. Most patients associated the daily application of laser with prompt relief of pain.

Antunes et al (2007), reported a randomized trial involving 38 hematopoietic stem cell transplantation (HSCT) patients into 2 groups LLLT (19) and Placebo (19) controls. A diode laser (InGaAlP, λ=660nm, P=50mW, ED=4J/cm², t=16.7s/point on 15 points, end with section area=0.196cm²) was used. The evaluation of OM was done using the Oral Mucositis Assessment Scale (OMAS) and the World Health Organization (WHO) scale. Blinded assessors assessed the outcomes from D-7 until neutrophil recovery. In the LLLT group, 94.7% of patients had an OM grade (WHO) lower ≤ grade 2, including 63.2% with grade 0 and 1, whereas in the controls
group, 31.5% of patients had an OM grade ≤ grade 2 ($P < .001$). Also the hazard ratio (HR) for grades 2, 3, and 4 OM was 0.41 (range, 0.22-0.75; $P = .002$) and for grades 3 and 4 it was 0.07 (range, 0.11-0.53; $P < .001$). Using OMAS by the calculation of ulcerous area, 5.3% of the laser group presented with ulcers of 9.1 cm$^2$ to 18 cm$^2$, whereas 73.6% of the control group presented with ulcers from 9.1 cm$^2$ to 18 cm$^2$ ($P=.003$). Pain score were not significant among two groups ($P=0.8$). Overall they concluded that LLLT was able to reduce the severity of oral mucositis. *Overall a well-designed trial but again small sample size is an issue.*

Schubert et al (2007),\textsuperscript{354} in a phase III randomized double-blind placebo-controlled clinical trial to determine the efficacy of low level laser therapy (GaAlAs) for the prevention of conditioning induced oral mucositis in patients undergoing HSCT, transplantation randomized 70 patients into 3 treatment groups: 650 nm laser(n=23), 780 nm laser (n=23) or placebo(n=24). Laser Energy density of 2J/cm$^2$ was delivered to the treatment area. Laser treatment began on the first day of conditioning and continued through day +2 post HSCT. Mucositis (Oral Mucositis Index) and oral pain (VAS only in 17 patients) were assessed on days 0, 4, 7, 11, 14, 18, and 21($\pm$1day) post HSCT. Result analysis revealed that the mean OMI scores varied most between groups at day 11 (placebo 24.3±2.9, 650 nm 16.7±2.9, 780 nm 20.6±2.9); and there was a significant difference between the placebo and 650 nm laser groups ($p=0.06$). In the end they concluded that the 650 nm wavelength reduced the severity of oral mucositis and pain scores compared to placebo while no significant difference found with 780 nm laser.

Jaguar et al (2007),\textsuperscript{355} in their study 24 patients who underwent HSCT received prophylactic LLLT (GaAlAs, $\lambda=660$nm, $P=10$mW, ED=2.5J/cm$^2$, $t=10$s/point) from the beginning of the conditioning regimen up to day +2. These patients were compared with 25 historical controls who didn’t receive the LLLT. The oral assessment was performed daily until day +30 for
mucositis (WHO scale) and pain (VAS). Results analysis revealed that all patients developed some grade of mucositis, but the time of onset of mucositis was delayed in LLLT than control i.e. 6.12 and 4.36 days respectively (P =0.01). Also mucositis healed early in laser treated patients. The maximum mucositis occurred between day +2 and day +6 with healing by day +25 in the control group and between day +2 and day +7 with healing by day +14 for the LLLT group (P = 0.84). Laser therapy also reduced oral pain duration from 5.64 to 2.45 days (P = 0.04), and incidence of morphine consumption in laser and control i.e. 4 vs 10 (P =0.07). But the initiation of morphine consumption day and parenteral nutrition use was almost equal in both the groups. Non-randomized study, retrospective control, no blinding and also small sample size were major limitations of this study.

Antunes et al(2008), in a case report of 11 HSCT patients who had developed the conditioning-induced oral mucositis (OM) grade 4 (WHO) or a total area of OM of 12 cm (OMAS) were treated with LLLT (InGaAlP, λ=660nm, P=50mW, ED=8J/cm^2, end with section area=0.196cm^2). The evaluation of OM was done using the Oral Mucositis Assessment Scale (OMAS) and World Health Organization (WHO) scale. They reported that grade IV mucositis recovered on average 6 days (3-12 days) from the beginning of the laser application.

Eduardo et al (2008), a survey of 30 patients undergoing HSCT (allogeneic or autologous) received LLLT (InGaAIP, λ=660nm, P=40mW) daily. Results analysis revealed that the incidence of grade III and IV mucositis was 23.3% and 3.3% respectively. They also reported that during most critical post-HSCT days (D+5 and D+8), incidence of grade I and II mucositis was 63.3% and 33.3% respectively and there was no incidence of grade III or IV mucositis.

Sardella et al (2008), in a literature report 24 HSCT patients received prophylactic LLLT from the beginning of the conditioning regimen up to day +2 and assessment was done daily
Review of Literature

until day +30. These were compared with historical controls (25). All patients developed some grade of mucositis but time of onset was delayed i.e. 6.12 vs 4.36 days, in Laser treated than control group patients. Also the maximum mucositis occurred between day +2 and day +6 with healing by day +25 in the control and between day +2 and day +7 with healing by day +14 for the laser group (P = 0.84). The duration of oral pain was reduced from 5.64 to 2.45 days (P = 0.04), and decreased the consumption of morphine (P = 0.07) with laser therapy.

Campos et al (2009), A case report showed improvement in QOL of a pediatric oncology patient with LLLT.

Kuhn et al (2009), carried out a randomized placebo-controlled trial in 21 children and adolescents with cancer receiving chemotherapy or HSCT using LLLT (n=9) (GaAlAs, λ=830nm (infrared), P=100mW, dose=4 J/cm) or placebo (n=12) (sham treatment). Patients were eligible as soon as they developed OM and received LLLT/sham treatment for 5 days. The OM grades were assessed using NCI-CTC scale before laser or sham application and thereafter until complete healing of the lesions. Result analysis showed that on day 7 after OM diagnosis, 1/9 of patients remained with lesions in laser group and 9/12 of patients in the placebo-control group (P=0.029). In the laser group, the mean of OM duration was 5.8+/–2 days and in the placebo group was 8.9+/–2.4 days (P=0.004). Authors concluded that laser therapy in addition to oral care can decrease the duration of chemotherapy-induced OM.

Silva et al (2010), conducted a randomized clinical trial of 42 HSCT (autologous or allogeneic) patients receiving high doses of chemotherapy/±total body irradiation. Patients were randomized into LLLT (InGaAlP, λ=660nm, P=40mW, and ED=4J/cm²) and control group. OM was assessed using WHO scale. Result analysis revealed that in the LLLT group, incidence of
grade I and II was 9.6% and 33.3% respectively, also 57.1% patients were free of OM whereas in the control group only 4.8% of patients free of OM.

_Cauwels et al (2011)_ conducted a pilot study to investigate the effects of LLLT (GaAlAs, $\lambda=830\text{nm}$, $P=150\text{mW}$) on pain relief and wound healing in chemotherapy-induced oral mucositis (OM) in a pediatric cancer patients. The energy released was adapted according to the severity of the OM lesions. The same protocol was repeated every 48hrs until healing of each lesion occurred. Assessment of OM (WHO Scale), oral pain (VAS) and functional impairment i.e. swallowing difficulty was done during each session of LLLT. Result analysis revealed that depending on the severity of OM, on average, 2.5 treatments per lesion in a period of 1 week were sufficient to heal a mucositis lesion. Also authors reported that immediate pain relief and improved wound healing resolved the swallowing difficulty in all cases.

**REVIEW STUDIES**

There were two review studies by _Genot and Klastersky (2005)_ and _Bjordal et al (2011)_

_Genot and Klastersky (2005)_ reviewed only six clinical studies results for the effects of LLLT on oral mucositis and its associated symptoms and concluded that the evidence of LLLT may be useful in decreasing the severity of chemotherapy-and radiotherapy-associated mucositis is substantial, even though controlled studies in the field of prevention are few and do not include large numbers of patients. The clinically controlled documentation of a beneficial effect in terms of pain control and healing for established lesions is even very less. Authors quoted that the evidence is clearly positive and should be further tested in large, well designed prospective trials.

_Bjordal et al (2011)_ did a systematic review and meta-analysis of randomized placebo-controlled trials of LLLT performed during chemotherapy or radiation therapy in head and neck cancer patients. They reviewed 11 randomized placebo-controlled trials with a total of 415
patients; methodological quality was acceptable at 4.10 (SD ± 0.74) on the 5-point Jadad scale. The relative risk (RR) for developing OM was significantly (P=0.02) reduced after LLLT compared with placebo LLLT (RR = 2.03 (95% CI, 1.11 to 3.69)). This preventive effect of LLLT improved to RR=2.72 (95% CI, 1.98 to 3.74) when only trials with adequate doses above 1J were included. For treatment of OM ulcers, the number of days with OM grade II or worse was significantly reduced after LLLT to 4.38 (95% CI, 3.35 to 5.40) days less than placebo LLLT. Oral mucositis severity was also reduced after LLLT with a standardized mean difference of 1.33 (95% CI, 0.68 to 1.98) over placebo LLLT. All studies registered possible side-effects, but they were not significantly different from placebo LLLT. In the end authors concluded that there is consistent evidence from small high-quality studies that red and infrared LLLT can partly prevent development of cancer therapy-induced OM. LLLT also significantly reduced pain, severity and duration of symptoms in patients with cancer therapy-induced OM. Very well reviewed study proved effectiveness of LLLT in prevention and treatment of Cancer therapy induced oral mucositis.

Bensadoun and Nair (2012)\textsuperscript{365}, in a very recent Systematic review and meta-analysis of 33 studies reported that LLLT reduced risk of oral mucositis with relative risk 2.45 [confidence interval 1.85-3.18], reduced duration, severity of oral mucositis and reduced number of days with oral mucositis (4.38 days, \(P=0.0009\)). They also reported that there was no difference between the red (630-670nm) and infrared (780-830nm) LLLT for reduction of risk of OM. Also pain reduction was reported with LLLT. They recommended that red or infrared LLLT with diode output between 10-100mW, dose of 2-3J/cm\(^2\) for prophylaxis and 4J/cm (maximum limit) for therapeutic effect, application on single spot rather than scanning motion should be used. In the
end they concluded that moderate-to-strong evidence exists in favor of LLLT at optimal doses for cancer therapy-induced oral mucositis.

GUIDELINES

MASCC and ISOO Guidelines in 2004 recommended that for centers capable of supporting the necessary technology and training, it suggested the use of low-level laser therapy in attempts to reduce the incidence of oral mucositis and its associated pain in patients at higher risk of cancer treatment associated oral mucositis. As for low-level laser therapy, the panel stated that results are difficult to assess and compare because of inter-operative variability and because clinical trials are difficult to conduct in that field. Nevertheless, panel was encouraged by the accumulating evidence in support of low-level laser therapy.16

OVERALL CONCLUSION

Despite of variability in types of laser and parameters used still evidence holds well in prevention and to some extent treatment of oral mucositis and its associated pain in various studies across the globe with almost every study is reporting positive outcomes this cannot happen by chance. Need of the time is to substantiate the effects of LLLT for the improvement of cancer therapy induced oral mucositis and also, to fix some uniform parameters across the globe to get optimal control on oral mucositis.