

## **MUCOSITIS**

### **Definition**

Mucositis is an inflammatory-like process of the oral mucosa due to radiation in head-neck oncology patients or chemotherapy.

It is characterised by atrophy of squamous epithelial tissue, vascular damage, and an inflammatory infiltrate concentrated at the basement region. Epithelial atrophy is followed by ulceration.

Mucositis is scored in four grades, I, II, III, and IV, for evaluation of treatment strategies and for communication purposes between oncologists. Grade III and IV mucositis is considered as severe, is painful and is characterized by ulcerative lesions, covered by fibrinous-inflammatory (pseudomembranous) exudate. The term “ulcerative/pseudomembrane mucositis” or the term “pseudomembranous mucositis” is used to describe these ulcerative lesions. Severe mucositis is a costly and dose-limiting complication of chemotherapy and head and neck radiotherapy.

Pain and dysphagia (restriction of oral intake) due to severe mucositis may further debilitate the already compromised cancer patient, while the loss of epithelial integrity will serve as site for secondary local infection and as portal of entry for the endogenous oral flora.

Mucositis is considered to be an inevitable but transient side effect of anti-neoplastic therapies.

### **Epidemiology**

During a course of curative radiation, about 80% of the patients will develop different grades of mucositis. In radiotherapy mucositis is an integral part in terms of morbidity, as during a course of curative radiation the majority of patients will develop pseudomembranous mucositis. The early radiation reaction causes local discomfort as well as difficulties in drinking, eating, swallowing and speech.

Hyperfractionation, accelerated fractionation and radiochemotherapy, although especially successful for the treatment of rapidly dividing tumours, result in higher rates of acute toxicity, especially mucositis. In head and neck radiotherapy these more aggressive regimens have been shown to improve local tumor control, but these are related to an increase in severe mucositis. This higher rates of acute toxicity result in higher levels of pain and difficulty in oral intake, and a significant worsening of the patient's quality of life. Recent data have shown that more than half of the head and neck cancer patients (56%) who receive altered fractionation radiotherapy, will experience more severe mucositis as compared to 34% of patients who receive conventional radiotherapy.

Severe mucositis can give rise to nutritional problems, while hospitalisation and nasogastric feeding may become necessary. Rates of hospitalisation due to severe mucositis, reported in several studies, were 32% for altered fractionation radiotherapy and overall 16% of all types of

radiotherapy. Furthermore, about 10% and up to 30% of patients, depending mostly on the type of treatment, may necessitate an interruption or a modification and prolongation of the course of radiotherapy because of severe mucositis. Interruptions and prolonged treatment adversely affect outcome and therapeutic effect.

In chemotherapy, the incidence and severity of mucositis is influenced by the type of anti-neoplastic drugs and related to tumour type. Based on these factors, between 20-100 % of the patients will develop severe mucositis during chemotherapy. In cancer chemotherapy severe mucositis will dramatically influence oral functions and general condition of the patient. Pain, sometimes requiring intensive analgesia, and restriction of normal feeding and drug intake are most important discomforts. In severe mucositis, secondary infection of the mucosal ulcers can provide a port of entry for micro-organisms into the circulation, leading to life-threatening septicaemia in myelosuppressed patients.

### **Clinical presentation**

The first clinical signs of radiation-induced mucositis occur at the end of the first week of a conventional seven-week radiation protocol (daily dose of 1.8 to 2.0 Gy, five times a week). A white discoloration of the oral mucosa, which is an expression of hyperkeratinisation of the epithelium, followed by erythema, is initially seen (figure 1). In other cases, a white discoloration maybe observed in combination with areas of erythema or erythema may appear first. The above clinical signs represent the grade I mucositis and are mostly asymptomatic. Towards the end of the second or around the third week of radiotherapy, small foci of ulceration can be observed, corresponding to the grade II mucositis. Patient complains of mild pain and can take soft diet. Severe, grade III mucositis presents as ulcers covered by pseudomembranes, affecting large areas of the oral mucosa (figure 2). Pseudomembranes are very painful to rub off, while the patient complains of severe pain and dysphagia (difficulty in oral intake) and can take liquids only. Grade IV mucositis represents even more severe ulceration, covering almost all mucosal surfaces. Patient complains of severe pain, can take liquids only or may necessitate nasogastric tube or parenteral support.

Mucositis is most severe in the soft palate, followed by the mucosa of the hypopharynx, floor of the mouth, cheek, base of the tongue, lips, and dorsum of the tongue. Patients with compromised oral mucous membranes secondary to alcoholism and/or excessive smoking exhibit the most severe mucosal lesions.

Mucositis generally persists throughout radiotherapy, and develops at its maximum grade at the end of the irradiation period. One to three weeks or more, depending on the severity, are needed for mucositis to heal, after the completion of radiotherapy.

Erythematous, ulcerated and xerostomic (dry) oral mucosa serves as site for the development of secondary infection. About one out of three patients are anticipated to develop

pseudomembranous candidosis during radiotherapy. The local inflammatory reaction caused by candidosis adds to the radiation-induced inflammatory process. According to some preliminary literature data, herpes virus-1 reactivation and infection may also complicate oral radiation-induced mucositis, aggravating the ulcerations (figure 3).

Chemotherapy-induced mucositis, initially seen between 3 and 7 days, after infusion of the anti-neoplastic drugs, presents as atrophy, followed by ulcerations within a few days. The maximum grade of mucositis is observed usually after 11 days, and could last for several days to weeks. Secondary local infection will delay healing.

### **Aetiopathogenesis**

Mucositis is basically a tissue reaction to the trauma of radiation or chemotherapy. Total dose, radiation portals, fractionation schedule, and type of ionising radiation as well as dose and type of chemotherapy agents affect the occurrence and severity of mucositis.

The pathogenesis of mucositis, being similar but not identical in both chemotherapy and radiation, is not fully understood.

The hypothesis proposed for the development of radiation- and chemotherapy-induced mucositis consider four consecutive phases: (1) inflammatory/vascular phase (free radicals and cytokines are released); (2) epithelial phase (reduced epithelial renewal-atrophy); (3) ulcerative/bacterial phase (colonisation by mixed flora, causing release of endotoxins, with further tissue damage by stimulation of cytokines). An interplay between the radiation- or chemotherapy-induced epithelial ulceration and bacterial flora is implied in this phase; (4) healing phase.

Factors that may contribute to the development of mucositis include the increase in inflammatory mediators, platelet activating factor in saliva, leukocyte adhesion to E-selectin or endothelial intercellular adhesion molecule-1 (ICAM-1) which promotes the radiation-induced inflammatory response in squamous epithelium, a decrease in the level of salivary epidermal growth factor and loss of protective salivary constituents.

A marked increase in the carriage rate of Gram-negative bacilli in the oropharynx (a/o. *Enterobacteriaceae*, *Pseudomonaceae*) has particularly been shown as a possible aggravating factor in the development of oral mucositis. Selective elimination of Gram-negative bacilli was associated with a reduction of radiation-induced pseudomembranous mucositis.

The most common infection in the oral cavity during or shortly after radiotherapy and chemotherapy is candidosis. Many patients become colonised intra-orally with *Candida albicans* during cancer therapy. The prevalence of positive *Candida* cultures increased from 43% at baseline to 62% at completion of cancer therapy and to 75% during the follow up period. Some believe that oral mucositis is aggravated by fungal infections. However, treatment of yeast and

Gram-positive cocci with topical anti-fungals and disinfectants failed to relieve such complications. Thus, many of the oral lesions observed during treatment do not seem to be due to candidosis or streptococcal infection. Finally, it should be mentioned that herpes simplex virus infection is not a significant contributing factor in irradiation mucositis, this is in contrast to the commonly seen herpes simplex virus reactivation following chemotherapy and radiochemotherapy patients.

The direct toxic effect of cytostatic agents on rapidly dividing cells of the oral epithelium result in atrophy, erythema and ulceration. Indirect stomatotoxic effects are caused by release of inflammatory mediators, loss of protective salivary constituents, and therapy induced neutropenia, in combination with the colonisation of bacteria, fungi and viruses on damaged mucosa which can result in secondary infections. Neutropenia, in chemotherapy, increases the risk for secondary infections.

### **Diagnosis**

The diagnosis of grade I mucositis is based on the presence of asymptomatic mucosal erythema, evaluated on clinical grounds, and need no treatment. It has to be differentiated from erythematous candidosis, a common infection during head and neck radiotherapy and antineoplastic chemotherapy, which needs antifungal treatment. The differentiation of mucositis from the infection can be done only on clinical grounds. Laboratory findings of a positive *Candida* smear do not assist in the differential diagnosis, given the high *Candida* spp. carriage level (up to 75%) of patients during antineoplastic therapies. Symmetrical erythemas, erythema located only on the central area of the dorsum of the tongue or bilateral angular cheilitis may denote the presence of candidosis.

Grade II mucositis, with small foci of ulcers, is also diagnosed upon the clinical presentation, while it has to be differentiated from an early intraoral herpetic infection or from a superimposed candidosis.

The most distressing grade III and IV mucositis is diagnosed upon its clinical presentation of superficial ulcerations covered by pseudomembranes (figure 4), that are very painful to be rubbed off. These pseudomembranous ulcerations are to be differentiated from pseudomembranous candidosis (figure 5), consisting of whitish, easy to rub off, pseudomembranes. Again, the laboratory isolation of yeasts from smears, taken from the lesions, may be helpful, but is not critical for the diagnosis. Pseudomembranous candidosis may be superimposed on the pseudomembranous ulcerations of mucositis and, in these cases, the differentiation is difficult.

Severe mucositis is important to be differentiated from the, often clinically identical, herpes simplex virus-1 reactivation and infection in neutropenic patients. Herpetic infection, if not diagnosed and treated promptly, may further aggravate mucositis and delay healing, thus

compromising the antineoplastic protocol (figures 6 - 7). Early initiation of ulcerative mucositis or herpes labialis may assist in suspecting a herpetic infection.

## **Treatment**

The Consensus Development Panel of the National Institutes of Health (Consensus statement, 1990) stated that no drugs can prevent mucositis, an opinion that still holds to date, though the evidence is that ice cooling can minimise chemotherapy-induced mucositis.

Consequently, treatment of mucositis is still limited to reduction of its severity. Oral care programs, relief of pain and discomfort, early diagnosis and treatment of concomitant secondary mucosal infections and/or strategies to eliminate micro-organisms, that are thought to promote or aggravate mucositis, are all engaged in its treatment.

For relief of pain and discomfort due to mucositis several anaesthetics, analgesics, and mucosal coating agents, acting as cytoprotectants, have been recommended.

Periodic rinses with topical anaesthetics such as viscous xylocaine (lidocaine) and benzydamine are often proposed. For relief of pain and resolution of mucositis, encouraging results have also been reported with the use of sucralfate suspensions, thought to form a protective barrier on the oral mucosa.

Antibacterials are also used to reduce mucositis. The potential beneficial effects of aqueous chlorhexidine rinses to control chemotherapy-associated oral mucositis has been reported, but it did not seem to control radiation mucositis. Besides, it may cause mucosal burning and irritation. Selective elimination of oral Gram-negative bacilli has been shown to have an ameliorating effect on the severity of radiation mucositis. The use of polymyxin E/ tobramycin/ amphotericin B (PTA)-containing lozenges, pastilles or paste were shown to reduce mucositis. Preliminary research data indicate that the administration of growth factors (granulocyte-macrophage colony stimulating factor, keratinocyte growth factor) and radioprotectors may reduce the severity of mucositis and promote healing. The reduction of mucositis and promotion of healing by growth factors is most likely due to stimulation of surviving stem cells, but this needs further study especially as these therapies may affect tumour response. This consideration is also applicable to the administration of the radioprotective agent amifostine during radiation treatment. A major flaw of most of the preliminary growth factor and radioprotector studies is that their trial design is at least questionable and the outcomes subject to debate. Nevertheless, the results of these preliminary studies are promising and may finally lead up, after repeated in high-quality randomised, placebo-controlled clinical trials, to modification of current oral care programs that are of limited efficacy in treating radiation mucositis.

## **Prognosis and complication**

Severe, grade III and IV mucositis causes pain and dysphagia and may debilitate the already compromised cancer patient. However, mucositis usually heals within one month after the completion of antineoplastic chemotherapy and head and neck radiotherapy, leaving no other significant side effect, and, thus, having a good prognosis.

Severe mucositis gives rise to nutritional problems, and may necessitate hospitalisation and nasogastric feeding, increasing the cost of antineoplastic therapy, while it seriously affects patient's quality of life.

The development of secondary local and systemic infection, which may threaten life in immunocompromised patients, is an important complication related to mucositis. Constant surveillance of the patient, with early and prompt diagnosis and treatment of the infection will minimize the effect of the above complication.

Another, most important complication of severe mucositis is its dose-limiting effect, the modification, the interruption or the prolongation of the antineoplastic therapy, adversely affecting the outcome and therapeutic effect.

## **Prevention**

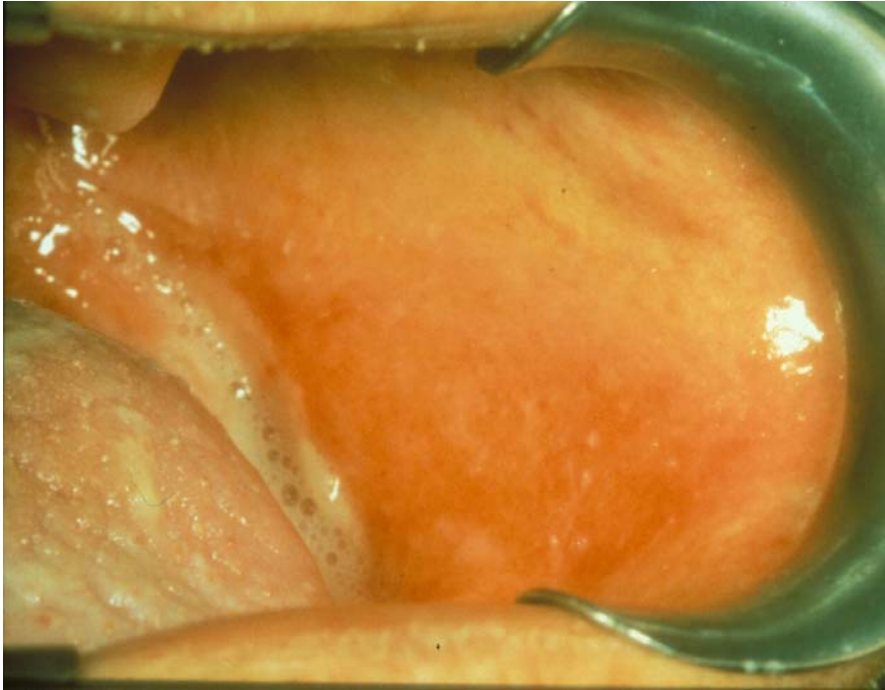
Mucositis is, at present, an inevitable side effect of antineoplastic therapies. Several strategies, including oral care programs and improved radiation treatment modalities, are available to prevent or reduce the incidence and the severity of mucositis.

Currently, most oral care programs aim at: removal of mucosal irritating factors, cleansing of the oral mucosa, maintaining the moisture of the lips and the oral cavity, relief of mucosal pain and inflammation. Although it has been suggested that good oral hygiene may reduce the development and severity of mucositis, no controlled studies of large numbers of patients have been undertaken yet. Nevertheless these recommendations still are a part of most protocols aimed to reduce the oral sequelae of head and neck radiotherapy and chemotherapy. To prevent iatrogenic mucosal damage, irritating factors such as sharp or rough fillings should be smoothed or polished prior to cancer therapy, and prosthetic appliances should be closely evaluated. Plaque control and oral hygiene should be maintained. Some recommend discouraging the wearing of dentures during radiotherapy. As denture surfaces may be colonised with *Candida* species, others recommend special attention to denture hygiene and removal of the appliance at least at night. In keeping with the scope of the elimination of irritating factors, the use of tobacco, alcohol, and spicy and acidic foods should also be discouraged. Patient should be instructed to take soft diet.

The use of various radiation treatment modalities and schedules of fractionation can play an important role in the prevention of mucositis. The use of high-energy photon beams, with the linear accelerators, provides a more homogenous dose distribution in and outside the target

area compared to the orthovoltage technique. This is due to the higher penetration of high-energy beams. Accelerated fractionation results in a more rapid onset of mucositis.

Early diagnosis and treatment of local infections, such as candidosis, and herpetic infection or infections due to Gram-negative bacilli, will benefit mucosal inflammation and minimize ulcerative lesions.



**Figure 1.** Grade I mucositis with erythematous changes of the left cheek mucosa. The demarcation between irradiated and non-irradiated tissue is obvious.

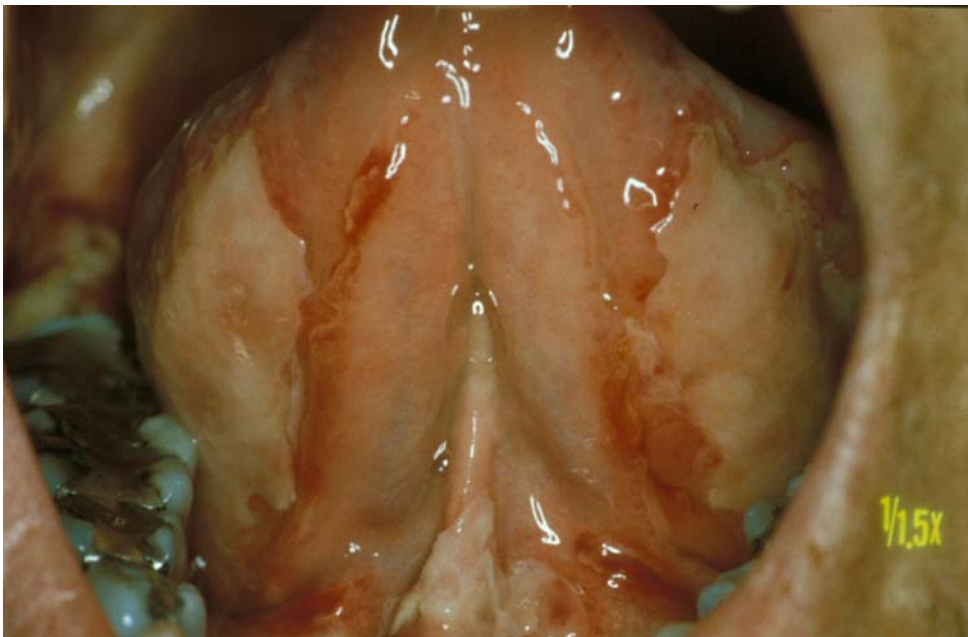


**Figure 2.** Grade III mucositis (paiful superficial ulcers covered by pseudomembranes) on the buccal mucosa of a 55 year old male (4th week of radiotherapy, 26 Gray, for the treatment of a squamous cell carcinoma of the tongue). (Viral culture for herpes simplex virus-1 infection was negative).

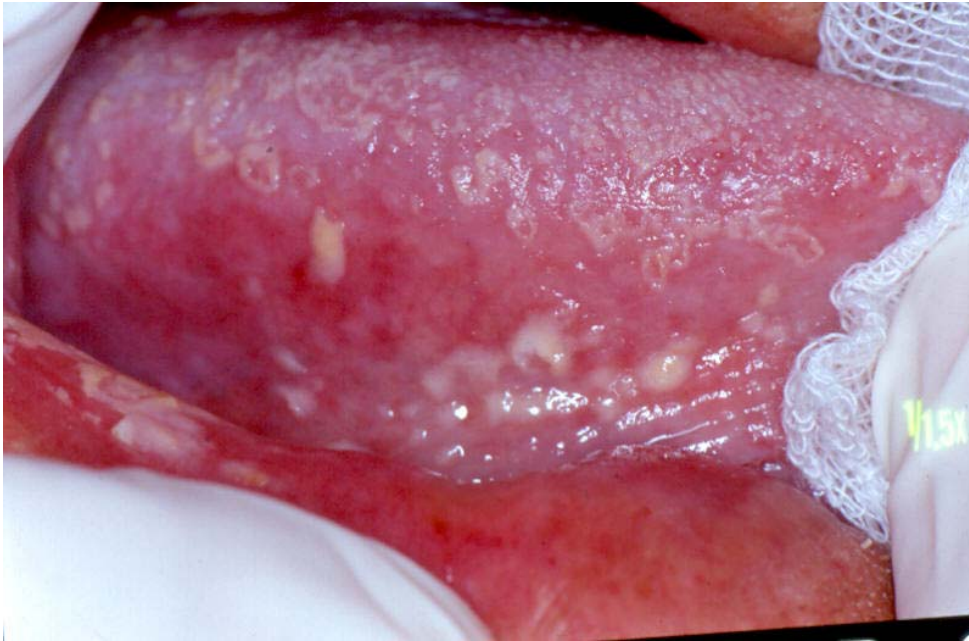




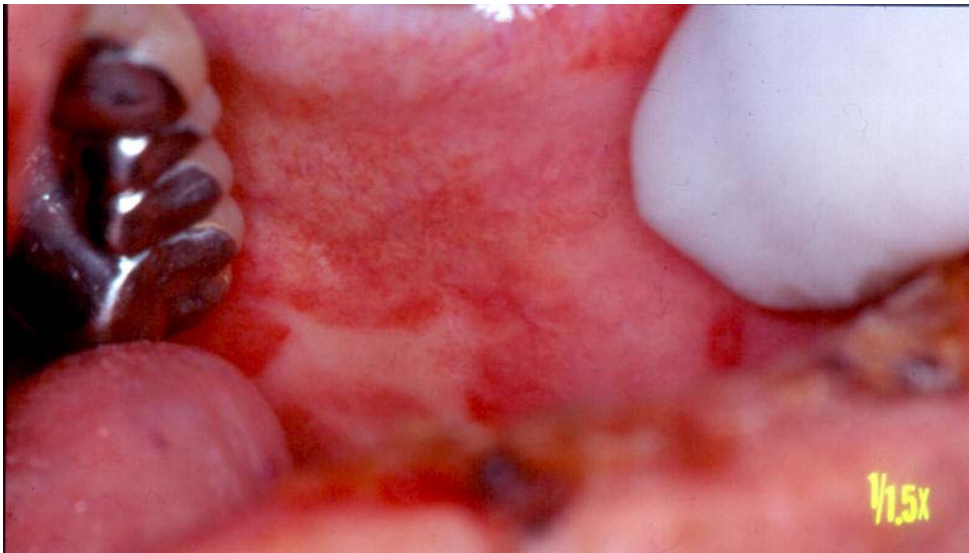
**Figure 3.** Painful superficial ulcers covered by pseudomembranes, clinically identical to grade II mucositis, on the buccal mucosa of a 74 year old male (7<sup>th</sup> radiotherapy fraction, 14 Gray, for the treatment of an oral squamous cell carcinoma). Viral culture and cytology smear were positive for herpes simplex virus-1 infection. Patient responded well to antiviral treatment and ulcers were diagnosed as of herpetic etiology. Radiotherapy was not interrupted.



**Figure 4.** Grade III mucositis (painful superficial ulcers covered by pseudomembranes) on the lateral borders of the tongue and floor of mouth of a 28 year old female during chemotherapy (9 days after infusion) during an autologous bone marrow transplantation.



**Figure 5.** Pseudomembranous candidiasis (whitish-yellowish candidal pseudomembranes) on the tongue and buccal mucosa (30<sup>th</sup> fraction of radiotherapy for the treatment of a squamous cell carcinoma of the floor of mouth). Patient complained of xerostomia and bad sensation, no pain.



**Figure 6.** Painful ulcerations, covered by pseudomembranes, clinically identical to grade III mucositis, on the buccal mucosa of a 67 year-old male with a non Hodgkin's lymphoma, 17 days after induction chemotherapy. Lesions were not healing, delaying the administration of the next chemotherapeutic scheme.



**Figure 7.** Same patient, as in figure 6. Multiple, haemorrhagic ulcerations and crusting on the lips. Cytology showed a herpetic infection and patient responded well to intravenous antiviral treatment.

### **Further reading**

- 1 Consensus statement. Oral complications of cancer therapies. NCI Monogr 1990; 9:3-8
- 2 Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy induced stomatotoxicity. Oral Oncol 1998; 34:34-43.
- 3 Vissink A, Jansma J, Spijkervet FKL, Burlage FR, Coppes RP. Oral sequelae of head and neck radiotherapy. Crit Rev Oral Med 2003; 14:199-212.
- 4 Vissink A, Burlage FR, Spijkervet FKL, Jansma J, Coppes RP. Prevention and treatment of the consequences of head and neck radiotherapy. Crit Rev Oral Med 2003; 14:213-225
- 5 Sonis ST, Eilers JP, Epstein JB, et al. Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Cancer 1999; 85:2103-2113.
- 6 Scully,C, Epstein J, Sonis, S. Oral mucositis: A challenging complication of radiotherapy, chemotherapy, and radiochemotherapy: Part 1, pathogenesis and prophylaxis of mucositis. Head Neck. 2003; 25:1057-1070 & Part 2, diagnosis and management of mucositis Head and Neck 2004; 26: 77-84