Oral Oncology 144 (2023) 106488

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Influence of the microbiome on radiotherapy-induced oral mucositis and its management: A comprehensive review

África Fernández Forné [a], María Jesús García Anaya [b], Salvador José Segado Guillot [b], Isaac Plaza Andrade [c], Lourdes de la Peña Fernández [d], María Jesús Lorca Ocón [b], Yolanda Lupiáñez Pérez [b], María Isabel Queipo-Ortuño [c,e,*], Jaime Gómez-Millán [b]

[a] Department of Radiation Oncology. Punta Europa University Hospital. Algeciras, Cádiz, Spain
[b] Department of Radiation Oncology, Virgen de la Victoria University Hospital, 29010 Málaga, Spain
[c] Intercenter Clinical Unit of Medical Oncology, Regional and Virgen de la Victoria University Hospitals, Biomedical Research Institute of Malaga (IBIMA)-CIMES-UMA, University of Malaga, 29010 Málaga, Spain
[d] Department of Radiology and Physical Medicine. School of Medicine, University of Málaga, 29010 Málaga, Spain
[e] Department of Surgical Specialties, Biochemical and Immunology, Faculty of Medicine, University of Málaga, 29010 Malaga, Spain

ARTICLE INFO

Keywords:
Oral mucositis
Radiotherapy
Pathogenesis
Microbiome
Head and neck cancer
Treatment

ABSTRACT

Radiation-induced mucositis is the most common, debilitating and painful acute toxicity associated with active treatment in head and neck cancer area, severely affecting more than 65% of patients. Oral microbiota significantly changes during cancer therapy and appears to be involved on its pathophysiology. This review aims to present a comprehensive update of new etiopathogenic factors and treatments that may decrease the incidence of mucositis, mainly modifications of dietary interventions to modify microbiome. Despite advances in recent years, its management is mainly symptomatic opioid-based with variable results on different substances analyzed for its prevention. Immunonutrition seems to play a significant role, particularly the supplementation of compounds such as fatty acids, polyphenols or selected probiotics have shown to promote commensal bacteria diversity and reduced incidence of ulcerative mucositis. Modification of the microbiome is a promising preventive treatment for mucositis although its evidence is still scarce. Large studies are needed to demonstrate the efficacy of interventions on microbiome and its clinical impact on radiation-induced mucositis.

Introduction

Radiotherapy alone (RT) or combined with chemotherapy (CT) is the cornerstone of treatment for squamous head and neck cancer (HNC) [1]. Combined treatment with RT and CT (CRT) has improved the prognosis of patients with advanced HNC [2]. However, CRT is associated with a higher rate of acute and late side effects [3] and a significant reduction in patient quality of life [4]. Radiation-induced mucositis (RIM) is the most frequent acute toxicity associated with CRT in head and neck tumors [5]. RIM refers to an inflammation of the mucosal lining epithelium of the digestive tract, caused by cytotoxic treatments, when rapidly dividing mucosal cells are killed and are not immediately replaced by new cells [6]. It has been estimated that most of the patients with HNC who undergo radiotherapy (RT) will experiment some degree of RIM throughout their cancer treatment [7], and at around 66–85% patients will suffer from severe RIM [7,8].

RIM represents a major clinical problem in oncology. Inflammation of the mucosa may cause moderate to severe pain, requiring the use of opioids in around 53% of cases [9]. In addition, pain can severely limit adequate nutrition, leading to significant weight loss that usually requires supplementary enteral feeding [8], with an increased risk of systemic infections and hospitalization [10]. Moreover, different studies have shown that RIM is associated with reduced social interaction, anxiety, depression and a decline in patient quality of life of the patients (QoL) [11]. Furthermore, RIM also has an important impact on medical resources, with a high hospitalization rate and use of emergency services [12]. Finally, RIM has prognostic implications in patients with HNC, being a common cause of unplanned interruptions of the treatment, favoring accelerated repopulation [13], decreasing treatment efficacy [14]. Additionally, it may induce consequential late effects, with swallowing difficulties and long-term fibrosis [15,16] that may increase the incidence of competitive cancer deaths.

* Corresponding author at: Department of Surgical Specialties, Biochemical and Immunology, Faculty of Medicine, University of Málaga, 29010 Malaga, Spain.
E-mail address: iqueipo@uma.es (M.I. Queipo-Ortuño).

https://doi.org/10.1016/j.oraloncology.2023.106488
Received 5 April 2023; Accepted 29 June 2023
Available online 1 July 2023

Despite the recent advances in the last decade, the incidence of mucositis has not decreased. The advent of intensity-modulated radiotherapy (IMRT) has been a major advance in HNC treatment by reducing radiotherapy toxicity in patients with HNC, decreasing irradiation of normal structures, with a consequential reduction of chronic effects such as xerostomia [17]. However, IMRT has not substantially reduced acute side effects, and patients treated with IMRT exhibit a similar rate of moderate-intense mucositis than patients treated with 3D-planning RT. On the other hand, scientific evidence has not shown any benefit in the prevention or treatment of RIM with any investigated agent or drug [5].

Finally, in a healthy individual, oral microbiota (MB) contains about 34 different taxonomic units [18] with abundance of the Proteobacteria, Bacteroidetes and Firmicutes phylum [19], providing a well-balanced ecosystem for periodontal maintenance [20]. The MB is a dynamic system, with constant alterations in its proportion and composition throughout the life of the host. This complex balance can be broken, due to host factors (e.g., immune system, genetic polymorphisms) or extrinsic factors (e.g., pharmacological treatment, diet, tobacco/alcohol exposure) causing a dysbiosis [18].

Several studies of the MB during cancer treatment have shown that the MB changes significantly during cancer therapy (e.g., via a shift to pathogenic species or a reduction in oral microbial diversity) [18–21], and this suggests that a loss of specific commensal flora essential for the health of the oral epithelium may also be important to oral mucositis pathophysiology. In fact, changes in the oral microbiome can affect an important stimulator of the mucositis pathway, the innate immune response [22]. Influence of oral microbiome on RIM is characterized by the production of inflammatory cytokines that are able to induce progression and aggravation of mucositis worsening the patienťs quality of life [23]. At the same time, several studies have described the positive effects of probiotics on the course of RIM [24]. Then, understanding the impact of radiation on the composition of the oral microbiota could help predict the course of RIM and the therapeutic use of probiotics in its management.

This review aims to discuss new etiopathogenic factors, and treatments based on these targets that may decrease the incidence of mucositis, mainly modifications of dietary interventions to modify microbiome.

Methods

The search strategy aimed to include articles related to the development of mucositis in head and neck patients treated by RT, the implication of microbiota on the course of the disease as well as on treatment and its toxicity, and the treatment of the mucositis. From 2001 through March 2023, a literature review was completed using the PubMed, Web of Science, Scopus and EMBASE electronic databases to identify relevant articles published in English. To perform the search we conducted a free-text search using these keywords in the title or abstract: “head and neck cancer” coupled with the term “radiotherapy”, “radiotherapy-induced mucositis”, “microbiota-oral cavity”, “intestinal dysbiosis”, “microbiome”, “malnutrition”, “toxicity”, “mucositis treatment”, “dietary interventions”, as well as thesaurus descriptors search using MeSH and Emtree (adapted for the selected databases). Articles were included if defined the oncology treatment received and the treatment-related toxicities experienced by the patients, the association of oral and gut microbiota dysbiosis with oral mucositis and their treatment, including nutritional intervention that affect this microbiota. In the same way, articles were excluded by abstract or full text due to their irrelevance to the analyzed topics. Finally, the references of the selected articles were also reviewed to identify any other studies that met the inclusion criteria.

Radiation induced mucositis

The first description of RIM appeared in 1980 and was characterized as an ionizing radiation toxicity after an injury to the normal tissue [25]. RIM was initially considered a simple process of inflammation; however, the complex pathogenesis process that take place in the oral and pharyngeal mucosa exposed to radiation are not still fully understood. The clinical manifestations of RIM consist of the appearance of a painful erythema in the irradiated mucosa that can progress to ulceration during the week 1 or 2 of treatment, after a cumulative dose of 10–15 Gy [26].

During week 3 (corresponding to a dose of 30 Gy), non-coalescent ulcers are observed, and pain intensifies rapidly. Subsequently, severe mucositis develops, manifesting as coalescent ulcers with deep ulceration that penetrates the submucosa [27], causing pain that often requires narcotic analgesics for its control [28]. These ulcers are prone to secondary infection, especially in neutropenic patients. Finally, healing occurs approximately 2–4 weeks after completion of therapy.

Sonis et al. [29] described the chronological development stages of RIM as a five-phase overlapping process of initiation, upregulation and message generation, signaling and amplification of the inflammation, ulceration, and healing. Initiation of mucositis starts shortly after the first administration of RT or CT. Generation of reactive oxygen species (ROS) induce an indirect DNA damage, leading basal to epithelial cell death by apoptosis and release of endogenous damage-associated pattern molecules (DAMPS) [30]. During this stage, ROS and DMAPs signaling induce an inflammatory response, promoting the activation of NF-kB. The transcription factor NF-kB is an important regulator of the inflammatory response, inducing the transcription of different genes involved in inflammation [31], such as pro-inflammatory cytokines (TNF-α, IL-β, IL-6) [32], cell adhesion molecules, stress responders such as cyclooxygenase-2 (COX-2) or inducible nitric oxide synthase (i-NOS), and cytokine modulators. In the amplification phase, the effectors produced in the previous phase led to an amplification of the injury signal. The released pro-inflammatory cytokines initiate the activation of mitogen-activated protein kinase (MAPKs) and COX-2 that activates different metalloproteinases (MMPs) and maintain the activity of NF-kB, perpetuating local inflammation through a positive-feedback loop mechanism [31]. As a consequence, severe damage to basal membrane integrity is produced and the formation of pseudomembranous lesions that converge are observed, producing ulceration of the mucosa. During this phase, microorganisms may invade the tissue leading to mononuclear-infiltrating cells-mediated inflammation [22], that release additional proinflammatory cytokines. In the healing process, the epithelium margins migrate as a consequence of extracellular matrix (ECM) signals, the activation of growth factors (epithelial growth factor and keratinocyte growth factor) [29] and anti-inflammatory cytokines as IL-10 and IL-11 [33], inducing tissue re-epithelization.

Clinical predictive factors

RIM has been traditionally associated with clinical, treatment, and patient related factors. The most studied clinical factors are the tumor stage, location, and the type of treatment. In a retrospective study of 80 patients, Tao et al. [34] found that patients with lymph node involvement presented higher rates of severe RIM ($p = 0.007$) compared with those without lymph node involvement, presenting the first group a significantly higher dose to the parapharyngeal space. Tumor location has also been associated to mucositis, showing a recently published prospective study of 1250 patients with locally advanced HNC that patients with lymph node involvement, oral cavity and oropharynx subsites presented a significantly higher rate of RIM ($p = 0,01$) [35].

The severity of RIM has been consistently associated with different treatment factors, such as the total dose radiotherapy, daily fraction size of radiation, volume of irradiated mucosa [35,36], and combination of RT with platinum-based CT (CRT) [37,38]. A cumulative dose of 20–30 Gy to the oral cavity has been shown to induce mucositis [8], with an increase of four times in RIM when a mean dose of 50 Gy is reached [39]. Regarding daily fraction size, the weekly dose rate of treatment was proven to determine mucosal reaction, with a significantly higher

incidence of RIM when a cumulative dose of 10.1 Gy (five fractions per week) to the oral cavity was reached [8]. Furthermore, an estimated significant increase in the risk of RIM was observed when an oral cavity volume of at least 21 cc was irradiated. Finally, treatment with CRT increases the risk RIM, with significantly higher rate and longer duration of RIM occurring after CRT compared with RT alone [35,40].

Additionally, different factors related to the patient have been linked to mucositis development. Several studies have shown that the consumption of tobacco has been linked with both increased prevalence and severity of RIM [36,37,41]. Other factors that have been traditionally associated to RIM are poor dental status [12], comorbidities [15,42] (such as diabetes mellitus and renal dysfunction), extreme ages [43], female gender [41], extreme body mass index (BMI) [44], and genetic polymorphism [45,46], among others.

Oral microbiome and mucositis

The oral cavity and pharynx contain one of the most singular MB of the human body [47]. It presents important variations according to different environmental influences (Figure 1), such as oxygen [19], the pH of the saliva, the type of water that is drunk [48] and the diet that is eaten [49], being unique in each individual [50]. Although the healthy oral MB has not been completely characterized, the finding of overall similarities among different niches of the oral cavity with similar MB composition, at all but the lowest taxonomic level, has made different authors to consider oral cavity and part of the oropharynx as an individual habitat [48,51]. Two main somatotypes have been identified with abundance of the Proteobacteria genera *Neisseria* and *Haemophilus*, and the other one the Bacteroidetes genus *Prevotella* and Firmicutes genus *Veillonella* respectively, that may represent healthy compositions of the MB [19]. Finally, other scarcely present non-bacterial oral microbes have been described as part of the oral MB, such as fungi in a proportion $< 0.1\%$, virus, protozoa and archaea [19].

Impairment of the salivary antimicrobial system as a result of oral dysbiosis has been hypothesized as an important cause of periodontitis [52,53], considered as the major cause of tooth loss in adults [54]. Inflammatory periodontal disease and poor dental health prior to CRT is known to be an environmental risk factor for radiation and chemotherapy induced oral mucositis [55] and pathogen microbiome colonization [35]. Thus, preventing measures such as a good oral hygiene, and a professional dental examination before CRT are recommended [5].

Exposure to anti-cancer therapies is extensively related to changes in the oral microflora (Figure 2). This can be caused directly by the damage of the cytotoxic treatment to bacteria in the oral cavity, or indirectly through disruption of the mucosal lining and the immunological balance [56]. Oral microbiota has been implicated in the pathogenic development of mucositis. In the initial stages, different substances released as a consequence of cells that have entered apoptosis or necrosis after first doses of RT (DAMPs, HMGB1) can be attached to Toll-like receptors (TLRs) that are, in turn, stimulated by lipopolysaccharides derived from microbial populations, initiating the inflammatory cascade through the activation of the NF-kB, TNF-α and increased IL-6 [22]. Later, as the damage to the mucosa progresses, an increase in membrane permeability will occur, with activation of immune response that amplifies the severity and duration of the oral mucositis. It seems that in this last phase, the immune system's recognition of the molecular patterns associated with pathogens (PAMPs) expressed by the microbiota may also induce and activate transcription of the NF-kB factor [57],

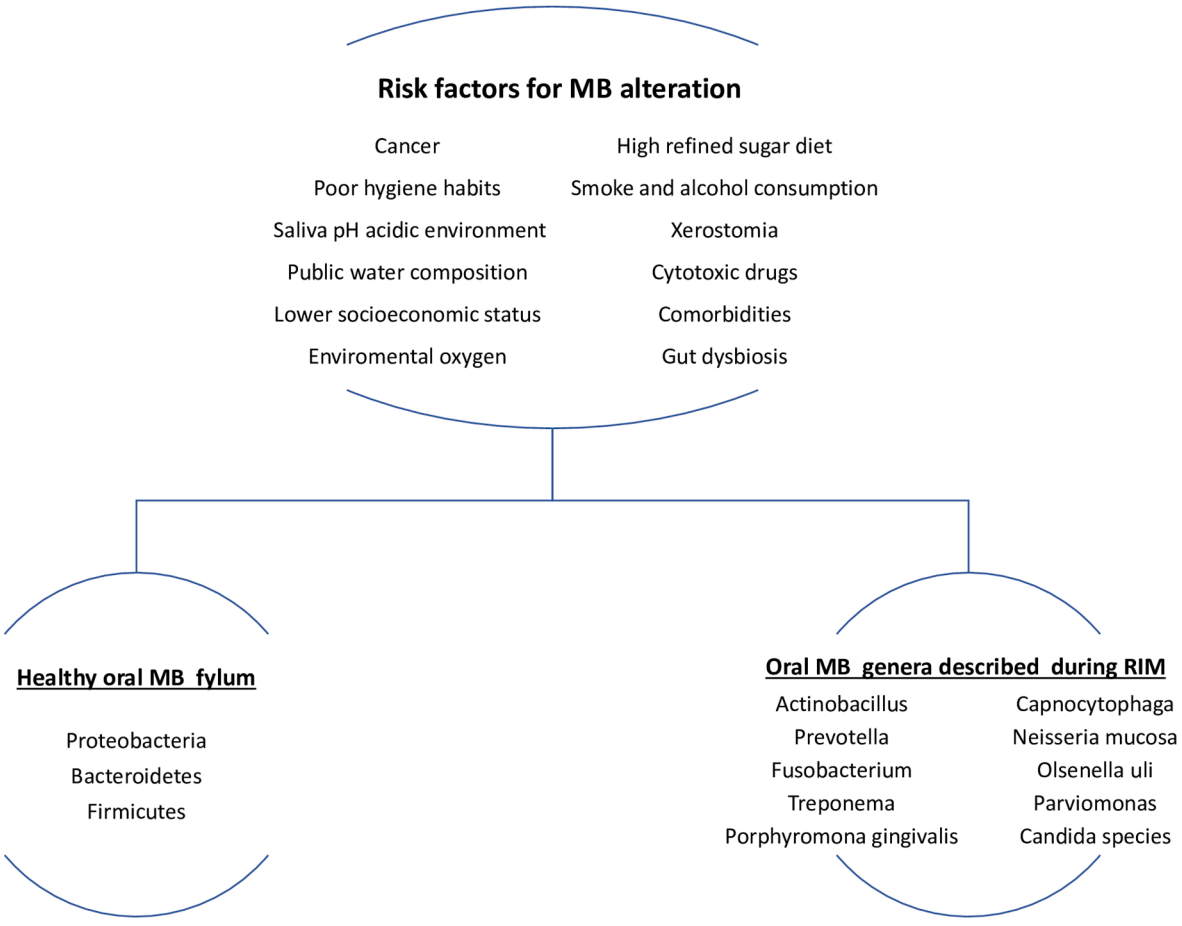

Figure 1. Description risk factors for microbiome (MB) alteration and description of principal healthy oral phylum and oral microbiome genera described during radiation induced mucositis (RIM).

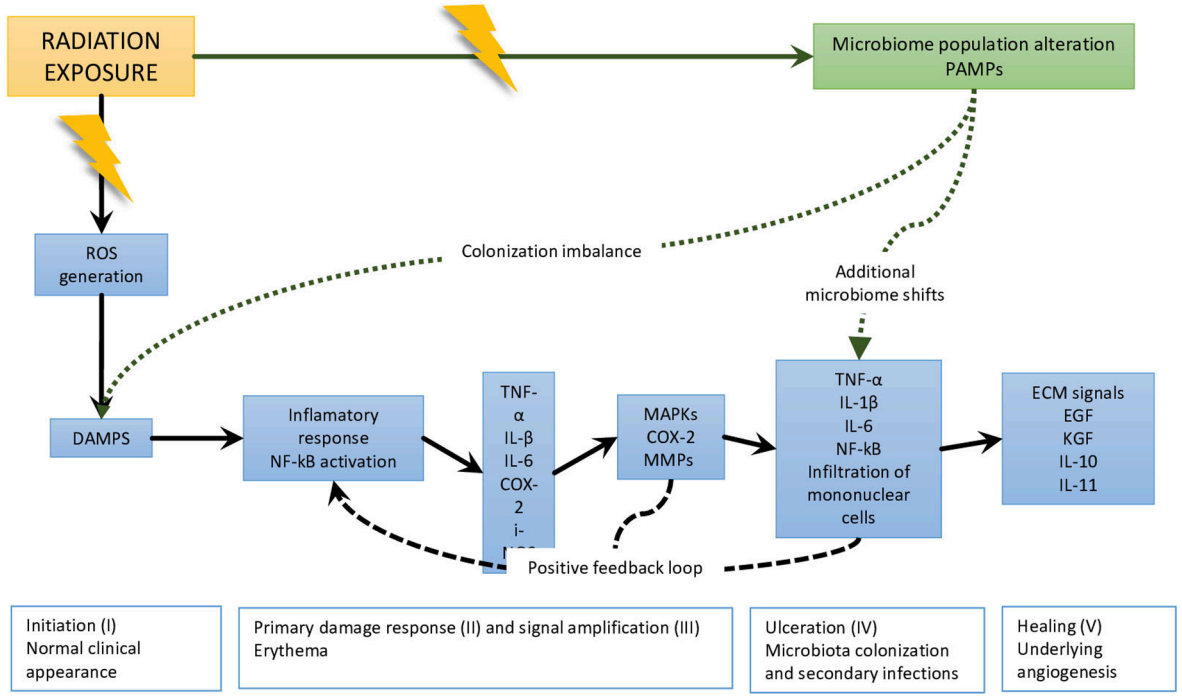

Figure 2. Pathophysiology of radiotherapy-induced oral mucositis and the influence of the microbiota on different phases of the process. The exposure to radiation treatment leads to an alteration in the microbial populations (previously affected by a variety of factors) with a reduction in diversity and an increase in anaerobic and gram-negative bacteria. On the other hand, it stimulates the generation of ROS that in turn causes direct damage to the tissue and initiates (I) an inflammatory cascade through the activation of transcription factors as NF-kB (II). At this point, bacterial colonization is altered, initiating microbial adhesion and dysbiosis. This process triggers the generation of proinflammatory cytokines that amplify signals (III) and the activation of stress factor responders leading to cellular apoptosis. The release of these pro-inflammatory cytokines induces a positive feedback loop that keeps the NF-kB mediated inflammatory response activated. During these phases, mucosal damage occurs leading to ulceration with the appearance of pseudomembranous lesions and altered permeability allowing the entry and colonization of pathogenic and opportunistic bacteria which continue to promote the inflammatory cascade and secondary infections impairing the healing capacity of the mucosa. Finally, signals from the extracellular matrix induce the generation of epithelial growth factors allowing angiogenesis so the healing phase is initiated (V). ROS: Reactive Oxygen Species. PAMPs: Molecular Patterns Associated with Pathogens. DAMPS: Endogenous Damage-Associated Pattern Molecules. NF-kB: Nuclear Factor kappa B. TNF-a: tumor Necrosis Factor a. IL: Interleukin. COZ-2: Cyclooxigenase-2. I-NOS: Inducible nitric Oxide Synthase. MAPKs: Mitogen-Activated Protein Kinase. MMPs: Metalloproteinases. ECM: Extracellular Matrix. EGF: Epidermal Growth Factor. KGF: Keratinocyte Growth Factor.

amplifying inflammatory response. Other plausible explanations that associate MB with RIM are changes in the adhesive properties of bacterial populations [58], a lower healing capacity in the presence of altered MB [59] or the induction of different immune responses depending on the bacteria that have colonized the mucosa [60,61].

Different clinical studies with HNC patients have explored the relationship among the dose of radiation, microbial changes and severity of mucositis. Hu et al. [62] observed that RT induced changes in the relative abundance of different microbial species before and after RT, with a negative correlation between radiation doses and the oral microbial richness. Zhu et al. [63] sequenced the dynamic changes in the oropharyngeal microbiota in patients irradiated for nasopharyngeal cancer and found a marked increase in the presence of gram-negative bacteria. Likewise, patients with severe oral mucositis had less bacterial diversity and a greater relative abundance of *Actinobacillus* compared with those with absence of mucositis or mild mucositis. Hou et al. [64] studied the microbiota of the oropharyngeal mucosa in patients treated with CRT or RT for nasopharyngeal carcinoma. In this study, the authors did not observe significant changes in diversity throughout the course of treatment, although some bacteria such as *Prevotella*, *Fusobacterium*, *Treponema* and *Porphyromon*a, showed differences in their abundance during treatment, coinciding with peaks of mucositis. Finally, Vesty et al. [65] confirmed the correlation of obligate and facultative anaerobic and gram-negative bacilli with mucositis, noting that the presence of pathogens as *Capnocytophaga leadbetteri*, *Neisseria mucosa*, *Olsenella uli* or *Parviomonas* prior to CRT were correlated to a higher grade of mucositis. In summary, although a specific pattern of MB alterations has not been demonstrated, the current evidence suggests that alterations in the MB compositions are associated with the onset and severity of oral mucositis [56,66].

On the other hand, although the associations between oral dysbiosis and RIM has been consistently shown, only one preclinical study has demonstrated a causal association between dysbiosis and mucositis, showing that germ-free mice treated with chemotherapy presented less mucositis, with lower expression of pro-inflammatory mediators and matrix metalloproteinases in the oral mucosa compared to specific pathogen-free mice [67]. This finding doesńt exclude a potential role of gut microbiota in oral mucositis, as germ-free mice are completely free of all microbes. Several studies have shown an alteration of the wound healing with delayed healing of oral ulcerations after co-culturing of oral MB microfilms and epithelial cell layer [56–59], with in vitro assays showing that *Porphyromona Gingivallis* and Candida spp. induce this inhibition of the wound closure [68].

Other factors associated to HNC carcinogenesis might increase the rate or duration of mucositis through interactions with MB. Tobacco and alcohol have the potential to shift the genera of bacteria in the oral mucosa, affecting the probability of presenting RIM during RT. Smoking may affect the distributions of numerous genera, with an enrichment of anaerobic lineages linked with periodontal disease in the oropharynx, and a lower relative abundance of the genera *Capnocytophaga*, *Peptostreptococcus* and *Leptotrichia* [69], inducing an increase in the severity of mucositis. Finally, other aggravating factors for microbiota-related mucositis are those related to the additional toxicities of radiotherapy. Xerostomia may influence a shift in oral microbiome composition linked with a higher percentage of Lactobacillus and candida spp. [57], and these alterations has been hypothesized to increase radiation induced

mucositis [22]. Finally, in recent years, randomized studies have shown that IMRT decreases xerostomia and salivary flow compared with 3DRT [17]. However, Shuurhuis et al. [70] have not found a difference in the microbial shift after IMRT compared with 3DRT treatment, with an increase of *Staphylococci*, Enteric rods and Candida spp.

A relationship between intestinal and oral cavity microbiota has been observed after treatments with cytotoxic agents, observing an increase in the presence of oral bacteria in the gut after treatment with high dose CT [71]. Preclinical studies with mice have also shown that the irradiation of the oral cavity induces a disruption an inflammation of the intestinal barriers [72]. Moreover, mice with a lower severity of radiation-induced oral mucositis were associated with reduced intestinal inflammation and increased expression of tight junction proteins in the intestinal mucosa [72]. Thus, oral mucositis is associated with major changes in the bacteria oral community, and translocation of dysbiotic bacteria from the oral cavity to the gut is likely to occur after cytotoxic treatment [56]. Besides, inflammatory changes in the gut associated to oral cavity mucositis may activate different systemic immune responses that may increase the intensity of mucositis.

Finally, intestinal dysbiosis has been identified as a possible causal factor of oral mucositis after RT. In a recent preclinical study, Al-Qadami et al. [56] have shown that after oral cavity irradiation with a single dose of 20 Gy, mice with antibiotic-induced gut microbiota depletion presented a short duration of oral mucositis, and lower levels of IL-6, IL-1b and TLR-4 in the tongue mucosa compared with mice not treated with antibiotics. Although a causal relationship between MB and oral mucositis (OM) exist, further studies are recommended to clarify the role of oral and/or intestinal MB in OM development.

Treatment of mucositis

The standard treatment for mucositis is based in preventive and symptomatic measures. Different guidelines have summarized the standard protocol on the management of mucositis, recommending, first of all, preventive measures based on a good oral hygiene, control of periodontal disease and professional dental examination prior to radiation treatment [5,28,73].

Local and systemic treatments

Several components have been explored to prevent RIM (Table 1), among them L-glutamine [74], benzydamine [75,76] and melatonin [77], showing a delayed onset of severe mucositis, reduced morphine consumption or a reduction in incidence and a shorter duration of RIM. Of these components, only benzydamine is recommended by clinical guidelines with level of evidence I [5]. Other compounds such as Palifermin (KGF-1) [78] and cryotherapy [79] are not widely recommended for the prevention of RIM [80], and should be used only under controlled clinical trials. The efficacy of intra-oral photobiomodulation (PBM) for prevention of oral mucositis has been reported in several studies with a low level of evidence [81].

In established mucositis, several treatments have been investigated (Table 2). The use of topic dexamethasone mouth rinse (0.1 mg/ml) for cases with multiple mucosal involvement, and systemic corticosteroids for recurrent or very symptomatic ulcers is recommended [28,73]. As coadjutant treatments, recent systematic review of the literature [82] has analyzed the effectiveness of gabapentin, pregabalin, nortriptyline, botulinum toxin and doxepin in treating mucositis. Of these treatments, only doxepin showed a reduction in oral pain due to RIM compared to placebo. It should be noted that most of the studies were methodologically of low quality and showed a high risk of bias. Other agents such as sucralfate has not shown any benefit [83], and its use is not recommended in the clinical practice.

Morphine as an opioid analgesic (natural opium alkaloids) confers its primary effects on the central nervous system as a specific μ-receptor antagonist. Its beneficial effect reducing RIM pain has been widely demonstrated with strong evidence [28,84,85] and it is still recommended its use when weak analgesics are not enough. Similar results have been obtained with the use of transdermal fentanyl, showing a significant pain reduction after the first day of application and even a significant improvement in their QoL [86]. In the absence of studies comparing efficacy against these molecules, opioid-based analgesia should remain the standard treatment in severe cases.

Nutritional support

Different nutritional compounds are currently under investigation for amelioration of RIM. The effect of combined formula with amino acids containing L-glutamine have been analyzed showing promising but variable results [74,87] in reducing grade 3–4 oral mucositis and improved adherence to treatment with concomitant CRT. Oral vitamin-D gel has been tested on a three-armed randomized trial [88] showing a significant reduction in severe RIM ($p = 0{,}014$) and a decrease in mean pain scores when compared with conventional treatment ($p = 0.0001$). Plantago lanceolata syrup has been reported [89] to significantly reduce the incidence of severe RIM at the end of RT compared with placebo ($p < 0{,}05$), decreasing the pain during RT ($p < 0{,}05$). Furthermore, another randomized controlled trial [90] with 60 HNC patients showed that pentoxifylline and oral vitamin-E significantly decreased the incidence ($p = 0{,}01$) and duration ($p = 0{,}002$) of severe RIM, which resulted in fewer hospitalizations and RT interruptions, without significant differences in time to onset of RIM or dysphagia. Finally, a *meta*-analysis [91] has reported that the prophylactic use of natural honey can be effective in reducing mucositis in HNC patients. It should be noted that most of these published studies present a high risk of bias due to significant statistical heterogeneity (mixed patient population, small sample size, and different sources), and these results should be interpreted with caution. In summary, different substances have shown to improve the rates of mucositis induced by RT in HNC patients. However, well designed randomized studies are needed to confirm these findings.

Malnutrition has negative consequences in wound healing over different process [92] such as fibroblast proliferation, angiogenesis,

Table 1
Evidence for interventions to prevent RIM.

Agent	Route of administration	Effect	Level of evidence	Recommended	Suggested
Mouthwashes with oral solutions	Oral	Topic	III	YES	YES
L-Glutamine	Oral	Systemic	II	NO	YES
Cryotherapy	Oral	Topic	II	NO	NO
Benzydamine	Oral	Topic	I	YES	YES
Celecoxib	Oral	Systemic	II	NO	NO
Misoprostol	Oral	Topic/Systemic	III	NO	NO
KGF-1†	Intravenous	Systemic	Not recommended	NO	NO
Melatonin	Oral	Systemic	II	–	–
PBM††	Oral	Topic	II	YES	YES
Honey	Oral	Topic/Systemic	II	YES	YES

† Palifermin. ††Photobiomodulation.

Table 2
Evidence for interventions to treat RIM.

Agent	Route of administration	Effect	Level of evidence	Recommended	Suggested
Steroids	Oral	Topical/Systemic	III	NO	Yes
Morphine 0,2%	Oral	Topical	III	NO	YES
Morphine	Oral	Systemic	II	YES	YES
Fentanyl	Transdermal	Systemic	III	YES	YES
Doxepin	Oral	Topical	II	NO	YES
TCAs†	Oral	Systemic	II	NO	NO
Botulinum toxin	Oral	Topical	III	NO	NO
Sucralfate	Oral	Topical/Systemic	II	NO	NO

†Tricyclic antidepressants.

destruction of the extracellular matrix, loss of amino acids (such as glutamine and arginine), carbohydrate deficiency and a decrease in the immune response that promote the intensification of mucositis. Several studies have shown an association between malnutrition and RIM. Saito et al. [44] identified that patients with a BMI < 18.5 presented a statistically significant higher incidence of severe RIM compared to patients with a BMI ≥ 18.5. These results were confirmed by Chen et al. [37] in a longitudinal study of 77 patients in which patients with a lower BMI during RT were at high risk of developing severe RIM. As a result, adequate oral nutritional support may decrease the risk of moderate to severe oral mucositis [93]. Nishii et al. [55] reported that patients treated with enteral tube feeding during CRT showed a significantly lower incidence of grade 3 RIM compared with those treated with oral supplements. A recent prospective study [94] with 87 patients reported that early nutritional intervention during CRT was associated with less nutritional impairment, and a decrease in the incidence of moderate to severe RIM compared with patients without any nutritional intervention, with rates of 17.9% and 50% respectively ($p = 0.012$). Finally, Alhambra-Expósito et al. [95] confirmed these findings and reported a prevalence of severe RIM lower than 10% in patients with adequate nutritional support during RT treatment.

Microbiota modification

Modification of the state of dysbiosis to promote oral health, competing with pathogens for nutrients and stimulating the mucosal immune system, has been investigated. Different probiotics, which contains live strains from bacteria genera such as *Bifidobacterium, Lactobacillus* and *Streptococcus* has been shown to promote alpha diversity and oral health improvement [19]. In a rat model, administration of probiotics containing *Bacillus subtilis, Bifidobacterium bifidum, Enterococcus faecium* and *Lactobacillus acidophilus* has been shown to increase OM regression, reducing oral and intestinal inflammation [96]. Moreover, a recent systematic review has shown that probiotics reduced the risk of all grades of OM, more significantly in severe mucositis [24].

A recently randomized double-blind clinical trial [97] has been published with 93 patients with locally advanced nasopharyngeal carcinoma, evaluating the efficacy in the reduction of RIM of a combination of probiotics (*Bifidobacterium longum, Lactobacillus lactis* and *Enterococcus faecium*) during CRT, compared to placebo. In the per-protocol analysis, the experimental group showed a significant reduction in G2-G3 mucositis measured with CTCAE V4.0, showing a decrease from 54% to 17%, and from 45% to 15% respectively ($p = 0{,}001$). Moreover, patients treated with probiotics were able to maintain a more diverse gut microbiota, similar to healthy patients, compared to the control group. In a phase II trial [98], 77 nasopharyngeal cancer patients were randomly assigned to receive either a probiotic cocktail vs. placebo. Authors found that patients in the probiotic group showed a reduction in G3 and G4 RIM incidence rates, from 32,4% to 22.2% and 14,7% to 2,8%, respectively ($p < 0{,}01$), and also a reduction in the inflammatory response reflected on a decrease of CD8 + T cells (73,59% vs. 62,36%; $p < 0{,}01$). Finally, Lactobacillus brevis CD2 lozenges have been shown to reduce the severity and incidence of CRT-induced mucositis in HNC patients, with a mucositis rate of 52% compared with 77%, increasing the rate of anticancer treatment completion [99]. These results have been reproduced in a phase 1B trial, showing a 35% reduction in the percentage of days with ulcerative mucositis in patients treated with AG013 compared with placebo [100]. Finally, in a preclinical study with rats treated with platinum, those that received D-Methionine showed a significant attenuation of oxidative stress in the intestinal mucosa, with an increase in IL-10 ($p < 0.05$), and a higher abundance of Lactobacillus and Lachnospiraceae compared with the control group [101].

In summary, modification of the microbiota open-up new directions for research into the understanding and management of RIM that should be confirmed with robust randomized trials.

Immunonutrition

Immune response has a central role in the mucositis development after cell damage is caused by radiation. High consumption of proinflammatory foods (saturated fatty acids, fried food, added sugars…) induces persistent inflammation with a consequent increase of interleukins IL-1, IL-4, IL-6 and TNF-α [102], intervening in the initiation and promotion of RIM. Conversely, a low intake of fruits and vegetables has been associated with an increased risk of developing cellular DNA damage [103]. The antioxidant compounds found in vegetables reduce reactive oxygen species and participate in DNA repair [104]. One of the emerging approaches to ameliorate the immune response to induced cell damage and stimulate recovery from RIM is fatty acid supplementation. PUFAs (Poly-Unsaturated Fatty Acids) play an important role on anti-inflammatory and cell-immune mechanisms, as the synthesis of several signaling molecules such as prostaglandin and leukotrienes involved in oral health [105]. Omega − 3 fatty acids are poly-unsaturated fatty acids (PUFAs) characterized by the presence of a double bond, three atoms away from the terminal methyl group in their chemical structure. Increased levels of omega-3 may induce immunoregulation and down regulation of pro-inflammatory cytokines (TNF-a, IL-1, IL-6, NF-kB), reducing the amplification phase of the mucositis and tissue damage [106]. Omega-3 fatty acids have been tested against several diseases showing a favorable symptom relief for patients due to its anti-inflammatory, analgesic, anti-microbial and even wound re-epithelialization effects [107]. The effects of immunonutrition with omega-3 in HNC patients undergoing CRT are currently under initial clinical research phase. Two recent randomized double-blind trials, a phase-II [108] and the IMPATOX phase-III trial [109], have failed to demonstrate a reduction in severe OM although both observed in a subgroup analysis that the overall survival was significantly improved. However, it should be mentioned that in both trials, omega-3 based supplementation was administered exclusively for 5 days prior to each three-weekly chemotherapy cycle. Studies with continuous daily supplementation during CRT are needed to observe different results.

Phytochemicals, as polyphenols, are powerful natural antioxidants from plant sources contained in many fruits and vegetables, such as red fruits, grapes, garlic, curcuma or green tea. Polyphenols have shown immunomodulatory properties and are being investigated for its possible radioprotective role on mucosal cells. Flavonoids are a family of

polyphenolic compounds which are widespread in nature (vegetables), presenting a dose-dependent antioxidant action, and the capacity of conferring protection to healthy tissue without affecting tumor cells [110]. A randomized clinical trial showed a reduction in the severity of RIM ($p < 0,05$) and weight loss ($p = 0,029$) compared to placebo in HNC patients who underwent polyphenol rinses (propolis) during radiotherapy protocol [111] and a recent prospective study supported these results, showing a significative reduced incidence of ulcerative oral mucositis ($p = 0,039$) in patients who received phytochemical-rich vegetable and fruit juices supplementation [112]. In addition, the use of specific foods with high content of these compounds has been studied. The benefits of green tea (*camellia sinensis*) are gaining popularity as a powerful source of polyphenols (epigallocatechin-3-gallate) as daily rinse has been reported to preserve the oral mucosa in HNC patients [113]. Pomegranate (*punica granatum*), in particular its peel, is one of the fruits with the highest antioxidant and polyphenol content, groups containing anthocyanin pigments and hydrolysable tannins have been studied for their protective effect against radiotherapy-induced reactive oxidants. The extract of pomegranate has shown to reduce the extent of mucositis in the oral cavity in HNC patients [114]. In animal models, the administration of apigenin has shown to slow down radiotherapy-induced intestinal mucosal damage as well as to block NF-kB signaling pathway [115]. This radioprotective effect could be related to the preservation of gut microbiota composition after polyphenol supplementation [116]. Furthermore, polyphenols may have an indirect influence on oral mucosal environment through the alteration of MB populations. In a recent prospective study with healthy volunteers, after polyphenol supplementation during two weeks, *Streptococcus, Neisseria* and *Haemophilus* were the most abundant genera on salivary samples [117]. A reduction in fecal *Fusobacterium* levels and an increase in gut short-chain fatty acids (SCFA)-producing genera were observed [118]. New clinical investigations are necessary to confirm the benefits of polyphenols in the clinical setting and its potential to influence on oral MB.

SCFA, such as acetate, propionate, and butyrate, are bacteria metabolites generated from the fermentation of soluble fiber by the gut MB. Luminal SCFA is an important energy substrate for the colonic epithelium, which in turn assist in the homeostatic regulation of commensal microbial populations [119]. Butyrate limits intestinal inflammation by promoting the formation of the regulatory T cells (Tregs), reducing pro-inflammatory cytokines in macrophages [120]. Moreover, SCFA n-butyrate also has an immunomodulation role by blocking the activation of NF-kB pathways [120]. The effects of SCFA have not yet been tested in relation to the oral mucosa in vivo. However, the promising results in vitro studies and its influence on oral microbiota make SCFAs an attractive agent to be investigated.

Conclusion

The management and prevention of RIM remains a difficult challenge with devastating implications for patients. A better understanding of its pathogenesis will allow further development of new therapeutic approaches. Predictive risk factors are mostly clinical, with treatment based in symptomatic treatments. Interest in nutritional management and how it influences the MB has increased in the recent years, with the additional interest of being a proactive and cost-effective intervention compared with pharmacological management. There is sufficient evidence to support that oral and pharynx MB may have a key influence in aggravating RIM. Meanwhile, the role of gut microbiota still needs to be clarified. Clinicians should be aware of the importance of the MB and keep updated on the efficacy of interventions that can be done and treatments under development. A better understanding of MB as a causative role in RIM may open the door to personalized treatment of mucositis. Despite the many studies published in the literature in recent decades, few advances have been made and to date there is no effective or preventive treatment to alleviate RIM, it will be necessary to correct these limitations to achieve new improvements.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Chow L. Head and neck cancer. N Engl J Med 2020;382:60–72.
[2] Mody MD, Rocco JW, Yom SS, Haddad RI, Saba NF. Head and neck cancer. Lancet 2021;398(10318):2289–99.
[3] Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, Forastiere A AK. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. J Clin Oncol. 2008; 20(26(1)):3582-3589.
[4] Xiang M, Holsinger FC, Colevas AD, Chen MM, Le QT, Beadle BM. Survival of patients with head and neck cancer treated with definitive radiotherapy and concurrent cisplatin or concurrent cetuximab: A Surveillance, Epidemiology, and End Results-Medicare analysis. Cancer 2018;124(23):4486–94.
[5] Elad S, Cheng KKF, Lalla Rv, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2020;126(19): 4423–31.
[6] Cereda E, Caraccia M, Caccialanza R. Probiotics and mucositis. Curr Opin Clin Nutr Metab Care 2018;21(5):399–404.
[7] Elting LS, Cooksley CD, Chambers MS, Garden AS. Risk, Outcomes, and Costs of Radiation-Induced Oral Mucositis Among Patients With Head-and-Neck Malignancies. Int J Radiat Oncol Biol Phys 2007;68(4):1110–20.
[8] Sanguineti G, Gunn GB, Parker BC, Endres EJ, Zeng J, Fiorino C. Weekly dose-volume parameters of mucosa and constrictor muscles predict the use of percutaneous endoscopic gastrostomy during exclusive intensity-modulated radiotherapy for oropharyngeal cancer. Int J Radiat Oncol Biol Phys 2011;79(1): 52–9.
[9] Mortensen HR, Overgaard J, Specht L, et al. Prevalence and peak incidence of acute and late normal tissue morbidity in the DAHANCA 6&7 randomised trial with accelerated radiotherapy for head and neck cancer. Radiother Oncol 2012; 103(1):69–75.
[10] Panghal M, Kaushal V, Kadayan S, Yadav JP. Incidence and risk factors for infection in oral cancer patients undergoing different treatments protocols. BMC Oral Health 2012;12:22.
[11] Ozsoy S, Besirli A, Unal D, Abdulrezzak U, Orhan O. The association between depression, weight loss and leptin/ghrelin levels in male patients with head and neck cancer undergoing radiotherapy. Gen Hosp Psychiatry 2015;37:31–5.
[12] Al-Ansari S, Zecha JAEM, Barasch A, de Lange J, Rozema FR, Raber-Durlacher JE. Oral Mucositis Induced By Anticancer Therapies. Curr Oral Health Rep 2015;2(4): 202–11.
[13] Fenwick JD, Lawrence GP, Malik Z, Nahum AE, Mayles WPM. Early Mucosal Reactions During and After Head-and-Neck Radiotherapy: Dependence of Treatment Tolerance on Radiation Dose and Schedule Duration. Int J Radiat Oncol Biol Phys 2008;71(2):625–34.
[14] Graboyes EM, Kompelli AR, Neskey DM, et al. Association of Treatment Delays with Survival for Patients with Head and Neck Cancer: A Systematic Review. JAMA Otolaryngol Head Neck Surg 2019;145(2):166–77.
[15] Elad S, Zadik Y. Chronic oral mucositis after radiotherapy to the head and neck: a new insight. Support Care Cancer 2016;24(11):4825–30.
[16] van den Berg M, Rütten H, Rasmussen-Conrad E, et al. Nutritional status, food intake, and dysphagia in long-term survivors with head and neck cancer treated with chemoradiotherapy: A cross-sectional study. Head Neck 2014;36(1):60–5.
[17] Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): A phase 3 multicentre randomised controlled trial. Lancet Oncol 2011;12(2):127–36.
[18] Gugnacki P, Sierko E. Is there an interplay between oral microbiome, head and neck carcinoma and radiation-induced oral mucositis? Cancers (Basel) 2021;13: 5902.
[19] Willis JR, Gabaldón T. The human oral microbiome in health and disease: From sequences to ecosystems. Microorganisms 2020;8(2):308.
[20] Gao L, Xu T, Huang G, Jiang S, Gu Y, Chen F. Oral microbiomes: more and more importance in oral cavity and whole body. Protein Cell 2018;9(5):488–500.
[21] Mougeot JLC, Stevens CB, Morton DS, Brennan MT, Mougeot FB. Oral Microbiome and Cancer Therapy-Induced Oral Mucositis. J Natl Cancer Inst Monogr 2019;2019(53):lgz002..
[22] Vasconcelos RM, Sanfilippo N, Paster BJ, et al. Host-Microbiome Cross-talk in Oral Mucositis. J Dent Res 2016;95(7):725–33.
[23] Naidu MUR, Ramana GV, Rani PU, Mohan IK, Suman A, Roy P. Chemotherapy-induced and/or radiation therapy-induced oral mucositis - Complicating the treatment of cancer. Neoplasia 2004;6(5):423–31.
[24] Shu Z, Li P, Yu B, Huang S, Chen Y. The effectiveness of probiotics in prevention and treatment of cancer therapy-induced oral mucositis: A systematic review and meta-analysis. Oral Oncol August 2019;2020(102):104559.
[25] Peterson DE. Research advances in oral mucositis. Curr Opin Oncol 1999;11(4): 261–6.

[26] Sonis ST. Mucositis: The impact, biology and therapeutic opportunities of oral mucositis. Oral Oncol 2009;45(12):1015–20.
[27] Lalla Rv, Bowen J, Barasch A, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer 2014;120(10):1453–61.
[28] de Sanctis V, Bossi P, Sanguineti G, et al. Mucositis in head and neck cancer patients treated with radiotherapy and systemic therapies: Literature review and consensus statements. Crit Rev Oncol Hematol 2016;2016(100):147–66.
[29] Sonis ST. The pathobiology of mucositis. Nat Rev Cancer 2004;4:277–84.
[30] Agrawal A, Choudhary D, Upreti M, Rath PC, Kale RK. Radiation induced oxidative stress: I. Studies in Ehrlich solid tumor in mice. Mol Cell Biochem 2001;223(1–2):71–80.
[31] Pulito C, Cristaudo A, la Porta C, et al. Oral mucositis: The hidden side of cancer therapy. J Exp Clin Cancer Res 2020;39(1):1–15.
[32] Treister N, Sonis S. Mucositis: Biology and management. Curr Opin Otolaryngol Head Neck Surg 2007;15(2):123–9.
[33] Villa A, Sonis ST. Mucositis: Pathobiology and management. Curr Opin Oncol 2015;27(3):159–64.
[34] Tao Z, Gao J, Qian L, et al. Factors associated with acute oral mucosal reaction induced by radiotherapy in head and neck squamous cell carcinoma: A retrospective single-center experience. Medicine (United States) 2017;96:50.
[35] Maji A, Mandal B, Basu A. A prospective study to assess the predictive factors of radiation-induced oral mucositis in head-and-neck carcinoma and its impact on treatment outcome: Long-term results and lessons learned. Int J Med Sci Public Health 2020;9(3):209–13.
[36] Hansen CR, Bertelsen A, Zukauskaite R, et al. Prediction of radiation-induced mucositis of H&N cancer patients based on a large patient cohort. Radiother Oncol 2020;147:15–21.
[37] Chen SC, Lai YH, Huang BS, Lin CY, Fan KH, Chang JTC. Changes and predictors of radiation-induced oral mucositis in patients with oral cavity cancer during active treatment. Eur J Oncol Nurs 2015;19(3):214–9.
[38] Pereira IF, Firmino RT, Meira HC, Vasconcelos BCDE, Noronha VRADS, Santos VR. Radiation-induced Oral Mucositis in Brazilian Patients: Prevalence and associated factors. In Vivo (Brooklyn). 2019;33(2):605-609.
[39] Mazzola R, Ricchetti F, Fersino S, et al. Predictors of mucositis in oropharyngeal and oral cavity cancer in patients treated with volumetric modulated radiation treatment: A dose–volume analysis Rosario. Head Neck 2016;38(10):E815–9.
[40] Forastiere AA, Goepfert H, Maor MH, et al. Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer. N Engl J Med 2003;349(22):2091–8.
[41] Wardill HR, Sonis ST, Blijlevens NMA, et al. Prediction of mucositis risk secondary to cancer therapy: a systematic review of current evidence and call to action. Support Care Cancer 2020;28(11):5059–73.
[42] Mizuno H, Miyai H, Yokoi A, et al. Relationship between renal dysfunction and oral mucositis in patients undergoing concurrent chemoradiotherapy for pharyngeal cancer: A retrospective cohort study. In Vivo (Brooklyn) 2019;33:183–9.
[43] Eilers J, Million R. Prevention and Management of Oral Mucositis in Patients With Cancer. Semin Oncol Nurs 2007;23(3):201–12.
[44] Saito N, Imai Y, Muto T, Sairenchi T. Low body mass index as a risk factor of moderate to severe oral mucositis in oral cancer patients with radiotherapy. Support Care Cancer 2012;20(12):3373–7.
[45] Li PJ, Li KX, Jin T, et al. Predictive Model and Precaution for Oral Mucositis During Chemo-Radiotherapy in Nasopharyngeal Carcinoma Patients. Front Oncol 2020;10:596822.
[46] Nanda SS, Gandhi AK, Rastogi M, et al. Evaluation of XRCC1 Gene Polymorphism as a Biomarker in Head and Neck Cancer Patients Undergoing Chemoradiation Therapy. Int J Radiat Oncol Biol Phys 2018;101(3):593–601.
[47] Pasolli E, Asnicar F, Manara S, et al. Extensive Unexplored Human Microbiome Diversity Revealed by Over 150,000 Genomes from Metagenomes Spanning Age, Geography, and Lifestyle. Cell 2019;176(3):649–662.e20.
[48] Willis JR, González-Torres P, Pittis AA, et al. Citizen science charts two major "stomatotypes" in the oral microbiome of adolescents and reveals links with habits and drinking water composition. Microbiome 2018;6(1):218.
[49] Lassalle F, Spagnoletti M, Fumagalli M, et al. Oral microbiomes from hunter-gatherers and traditional farmers reveal shifts in commensal balance and pathogen load linked to diet. Mol Ecol 2018;27(1):182–95.
[50] Li K, Bihan M, Yooseph S, Methé B. Analyses of the Microbial Diversity across the Human Microbiome. PLoS One 2012;7(6):e32118.
[51] Lim Y, Fukuma N, Totsika M, Kenny L, Morrison M, Punyadeera C. The performance of an oral microbiome biomarker panel in predicting oral cavity and oropharyngeal cancers. Front Cell Infect Microbiol 2018;8:267.
[52] Haubek D. The highly leukotoxic JP2 clone of Aggregatibacter actinomycetemcomitans: Evolutionary aspects, epidemiology and etiological role in aggressive periodontitis. Apmis SUPPL 2010;130:1–53.
[53] Matarazzo F, Ribeiro AC, Feres M, Faveri M, Mayer MPA. Diversity and quantitative analysis of Archaea in aggressive periodontitis and periodontally healthy subjects. J Clin Periodontol 2011;38(7):621–7.
[54] Ahn J, Segers S, Hayes RB. Periodontal disease, Porphyromonas gingivalis serum antibody levels and orodigestive cancer mortality. Carcinogenesis 2012;33(5):1055–8.
[55] Nishii M, Soutome S, Kawakita A, et al. Factors associated with severe oral mucositis and candidiasis in patients undergoing radiotherapy for oral and oropharyngeal carcinomas: a retrospective multicenter study of 326 patients. Support Care Cancer 2020;28(3):1069–75.
[56] Al-Qadami G, van Sebille Y, Bowen J, Wardill H. Oral-Gut Microbiome Axis in the Pathogenesis of Cancer Treatment-Induced Oral Mucositis. Frontiers. Oral Health 2022;3(March).
[57] Vanhoecke B, de Ryck T, Stringer A, van de Wiele T, Keefe D. Microbiota and their role in the pathogenesis of oral mucositis. Oral Dis 2015;21:17–30.
[58] Laheij AMGA, de Soet JJ, von dem Borne PA, et al. Oral bacteria and yeasts in relationship to oral ulcerations in hematopoietic stem cell transplant recipients. Support Care Cancer 2012;20(12):3231–40.
[59] Vanlancker E, Vanhoecke B, Sieprath T, et al. Oral microbiota reduce wound healing capacity of epithelial monolayers, irrespective of the presence of 5-fluorouracil. Exp Biol Med 2018;243(4):350–60.
[60] Maynard CL, Elson CO, Hatton RD, Weaver CT. Reciprocal interactions of the intestinal microbiota and immune system. Nature 2012;489(7415):231–41.
[61] Li Y, Ye Z, Zhu J, Fang S, Meng L, Zhou C. Effects of Gut Microbiota on Host Adaptive Immunity Under Immune Homeostasis and Tumor Pathology State. Front Immunol 2022;13(March):1–15.
[62] Hu YJ, Wang Q, Jiang YT, et al. Characterization of oral bacterial diversity of irradiated patients by high-throughput sequencing. Int J Oral Sci 2013;5:21–5.
[63] Zhu XX, Yang XJ, Chao YL, et al. The Potential Effect of Oral Microbiota in the Prediction of Mucositis During Radiotherapy for Nasopharyngeal Carcinoma. EBioMedicine 2017;18:23–31.
[64] Hou J, Zheng HM, Li P, Liu HY, Zhou HW, Yang XJ. Distinct shifts in the oral microbiota are associated with the progression and aggravation of mucositis during radiotherapy. Radiother Oncol 2018;129(1):44–51.
[65] Vesty A, Gear K, Biswas K, Mackenzie BW, Taylor MW, Douglas RG. Oral microbial influences on oral mucositis during radiotherapy treatment of head and neck cancer. Support Care Cancer 2020;28(6):2683–91.
[66] Reyes-Gibby CC, Wang J, Zhang L, et al. Oral microbiome and onset of oral mucositis in patients with squamous cell carcinoma of the head and neck. Cancer 2020;126(23):5124–36.
[67] Gupta N, Quah SY, Yeo JF, Ferreira J, Tan KS, Hong CHL. Role of oral flora in chemotherapy-induced oral mucositis in vivo. Arch Oral Biol 2019;101:51–6.
[68] Haverman TM, Laheij AMGA, de Soet JJ, de Lange J, Rozema FR. Candida and Porphyromonas gingivalis: the effect on wound closure in vitro. J Oral Microbiol 2017;9(1):1328266.
[69] Wu J, Peters BA, Dominianni C, et al. Cigarette smoking and the oral microbiome in a large study of American adults. ISME J 2016;10(10):2435–46.
[70] Schuurhuis JM, Stokman MA, Witjes MJH, et al. Head and neck intensity modulated radiation therapy leads to an increase of opportunistic oral pathogens. Oral Oncol 2016;2016(58):32–40.
[71] Panebianco C, Andriulli A, Pazienza V. Pharmacomicrobiomics: exploiting the drug-microbiota interactions in anticancer therapies. Microbiome 2018;6(1):92.
[72] Fernandez-Gil B, Abdel Moneim AE, Ortiz F, et al. Melatonin protects rats from radiotherapyinduced small intestine toxicity. PLoS One 2017;12(4):e0174474.
[73] Peterson DE, Boers-Doets CB, Bensadoun RJ, Herrstedt J. Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. Ann Oncol 2015;26(Suppl. 5):v139–51.
[74] Tsujimoto T, Yamamoto Y, Wasa M, et al. L-glutamine decreases the severity of mucositis induced by chemoradiotherapy in patients with locally advanced head and neck cancer: A double-blind, randomized, placebo-controlled trial. Oncol Rep 2015;33:33–9.
[75] Ariyawardana A, Cheng KKF, Kandwal A, et al. Systematic review of anti-inflammatory agents for the management of oral mucositis in cancer patients and clinical practice guidelines. Support Care Cancer 2019;27:3985–95.
[76] Chitapanarux I, Tungkasamit T, Petsuksiri J, et al. Randomized control trial of benzydamine HCl versus sodium bicarbonate for prophylaxis of concurrent chemoradiation-induced oral mucositis. Support Care Cancer 2018;26(3):879–86.
[77] Lozano A, Marruecos J, Rubió J, et al. Randomized placebo-controlled phase II trial of high-dose melatonin mucoadhesive oral gel for the prevention and treatment of oral mucositis in patients with head and neck cancer undergoing radiation therapy concurrent with systemic treatment. Clin Transl Oncol 2021;23(9):1801–10.
[78] Henke M, Alfonsi M, Foa P, et al. Palifermin decreases severe oral mucositis of patients undergoing postoperative radiochemotherapy for head and neck cancer: A randomized, placebo-controlled trial. J Clin Oncol 2011;29(20):2815–20.
[79] Correa MEP, Cheng KKF, Chiang K, et al. Systematic review of oral cryotherapy for the management of oral mucositis. Support Care Cancer 2020;28:2449–56.
[80] Kusiak A, Alicjajereczek-Fossa B, Cichońska D, Alterio D. Oncological-therapy related oral mucositis as an interdisciplinary problem—literature review. Int J Environ Res Public Health 2020;17:2464.
[81] Ferreira AS, Macedo C, Silva AM, Delerue-Matos C, Costa P, Rodrigues F. Natural Products for the Prevention and Treatment of Oral Mucositis—A Review. Int J Mol Sci 2022;23:4385.
[82] Lefebvre T, Tack L, Lycke M, et al. Effectiveness of Adjunctive Analgesics in Head and Neck Cancer Patients Receiving Curative (Chemo-) Radiotherapy: A Systematic Review. Pain Med 2021;22(1):152–64.
[83] Dodd MJ, Miaskowski C, Greenspan D, et al. Radiation-induced mucositis: A randomized clinical trial of micronized sucralfate versus salt & soda mouthwashes. Cancer Invest 2003;21(1):21–33.
[84] Ehrnrooth E, Grau C, Zachariae R, Andersen J. Randomized trial of opioids versus tricyclic antidepressants for radiation-induced mucositis pain in head and neck cancer. Acta Oncol (Madr) 2001;40(6):745–50.
[85] Maria OM, Eliopoulos N, Muanza T. Radiation-Induced Oral Mucositis. Front. Oncol 2017;7:89.
[86] Guo SP, Wu SG, Zhou J, et al. Transdermal fentanyl for pain due to chemoradiotherapy-induced oral mucositis in nasopharyngeal cancer patients:

Evaluating efficacy, safety, and improvement in quality of life. Drug Des Devel Ther 2014;8:497–503.
[87] Shuai T, Tian X, Xu LL, et al. Oral glutamine may have no clinical benefits to prevent radiation-induced oral mucositis in adult patients with head and neck cancer: A meta-analysis of randomized controlled trials. Front Nutr 2020;7:49.
[88] Bakr IS, Zaki AM, El-Moslemany RM, Elsaka RO. Vitamin D oral gel for prevention of radiation-induced oral mucositis: A randomized clinical trial. Oral Dis 2021;27 (5):1197–204.
[89] Soltani GM, Hemati S, Sarvizadeh M, Kamalinejad M, Tafazoli V, Latifi SAH. Efficacy of the plantago major L. syrup on radiation induced oral mucositis in head and neck cancer patients: A randomized, double blind, placebo-controlled clinical trial. Complement Ther Med 2020;51:102397.
[90] Sayed R, el Wakeel L, Saad AS, Kelany M, El-Hamamsy M. Pentoxifylline and vitamin E reduce the severity of radiotherapy-induced oral mucositis and dysphagia in head and neck cancer patients: a randomized, controlled study. Med Oncol 2020;37:8.
[91] Tian X, Xu L, Liu X, et al. Impact of honey on radiotherapy-induced oral mucositis in patients with head and neck cancer: A systematic review and meta-analysis. Ann Palliat Med 2020;9(4):1431–41.
[92] Ghaly P, Iliopoulos J, Ahmad M. The role of nutrition in wound healing: An overview. Br J Nurs 2021;30(5):S38–42.
[93] Shu Z, Zeng Z, Yu B, et al. Nutritional Status and Its Association With Radiation-Induced Oral Mucositis in Patients With Nasopharyngeal Carcinoma During Radiotherapy: A Prospective Study. Front Oncol 2020;10:594687.
[94] Wei J, Wu J, Meng L, et al. Effects of early nutritional intervention on oral mucositis in patients with radiotherapy for head and neck cancer. QJM 2020;113 (1):37–42.
[95] Alhambra Expósito M, Herrera-Martínez A, Manzano García G, Espinosa Calvo M, Bueno Serrano C, Gálvez MM. Early nutrition support therapy in patients with head-neck cancer. Nutr Hosp 2018;35:505–10.
[96] Gerhard D, da Silva Simão de Sousa FJ, Andraus RAC, et al. Probiotic therapy reduces inflammation and improves intestinal morphology in rats with induced oral mucositis. Braz Oral Res 2017;31:e71.
[97] Jiang C, Wang H, Xia C, et al. A randomized, double-blind, placebo-controlled trial of probiotics to reduce the severity of oral mucositis induced by chemoradiotherapy for patients with nasopharyngeal carcinoma. Cancer 2019; 125(7):1081–90.
[98] Xia C, Jiang C, Li W, et al. A Phase II Randomized Clinical Trial and Mechanistic Studies Using Improved Probiotics to Prevent Oral Mucositis Induced by Concurrent Radiotherapy and Chemotherapy in Nasopharyngeal Carcinoma. Front Immunol 2021;12:618150.
[99] Sharma A, Rath GK, Chaudhary SP, Thakar A, Mohanti BK, Bahadur S. Lactobacillus brevis CD2 lozenges reduce radiation- and chemotherapy-induced mucositis in patients with head and neck cancer: A randomized double-blind placebo-controlled study. Eur J Cancer 2012;48(6):875–81.
[100] Limaye SA, Haddad RI, Cilli F, et al. Phase 1b, multicenter, single blinded, placebo-controlled, sequential dose escalation study to assess the safety and tolerability of topically applied AG013 in subjects with locally advanced head and neck cancer receiving induction chemotherapy. Cancer 2013;119(24):4268–76.
[101] Wu CH, Ko JL, Liao JM, et al. D-methionine alleviates cisplatin-induced mucositis by restoring the gut microbiota structure and improving intestinal inflammation. Ther Adv Med Oncol 2019;11:1–18.
[102] Bradshaw PT, Siega-Riz AM, Campbell M, Weissler MC, Funkhouser WK, Olshan AF. Associations between dietary patterns and head and neck cancer: The Carolina head and neck cancer epidemiology study. Am J Epidemiol 2012;175 (12):1225–33.
[103] Hua R, Liang G, Yang F. Meta-analysis of the association between dietary inflammatory index (DII) and upper aerodigestive tract cancer risk. Medicine 2020;99(17):e19879.
[104] Rodríguez-Molinero J, Migueláñez-Medrán BDC, Puente-Gutiérrez C, et al. Association between oral cancer and diet: An update. Nutrients 2021;13:1299.
[105] Gutiérrez S, Svahn SL, Johansson ME. Effects of omega-3 fatty acids on immune cells. Int J Mol Sci 2019;20(20).
[106] Lessa RC, Alves F de A, Fortunati E, Lu J. Oral mucositis in cancer and potential use of omega-3 free fatty acids in its management: A review. Biomedicines. 2021; 9:1531.
[107] Hashemipour MA, Barzegari S, Kakoie S, Aghahi RH. Effects of Omega-3 Fatty Acids Against Chemotherapy-induced Mucositis: A Double-blind Randomized Clinical Trial. Wounds 2017;29(12):360–6.
[108] Dechaphunkul T, Arundon T, Raungkhajon P, Jiratrachu R, Geater SL, Dechaphunkul A. Benefits of immunonutrition in patients with head and neck cancer receiving chemoradiation: A phase II randomized, double-blind study. Clin Nutr 2022;41(2):433–40.
[109] Boisselier P, Kaminsky MC, Thézenas S, et al. A double-blind phase III trial of immunomodulating nutritional formula during adjuvant chemoradiotherapy in head and neck cancer patients: IMPATOX. Am J Clin Nutr 2020;112(6):1523–31.
[110] Faramarzi S, Piccolella S, Manti L, Pacifico S. Could polyphenols really be a good radioprotective strategy? Molecules 2021;26(16):4969.
[111] Bolouri AJ, Pakfetrat A, Tonkaboni A, et al. Preventing and therapeutic effect of propolis in radiotherapy induced mucositis of head and neck cancers: A triple-blind, randomized, placebo-controlled trial. Int J Cancer Manag 2015;8(5):e4019.
[112] Chang HP, Huang MC, Lei YP, Chuang YJ, Wang CW, Sheen LY. Phytochemical-rich vegetable and fruit juice alleviates oral mucositis during concurrent chemoradiotherapy in patients with locally advanced head and neck cancer. J Tradit Complement Med 2022;12(5):488–98.
[113] Liao YC, Hsu LF, Hsieh LY, Luo YY. Effectiveness of green tea mouthwash for improving oral health status in oral cancer patients: A single-blind randomized controlled trial. Int J Nurs Stud 2021;121:103985.
[114] Thotambailu AM, Bhandary BSK, Sharmila KP. Protective Effect of Punica granatum Extract in Head and Neck Cancer Patients Undergoing Radiotherapy. Indian Journal of Otolaryngology and Head and Neck Surgery 2019;71(s1): 318–20.
[115] Begum N, Rajendra Prasad N, Kanimozhi G, Agilan B. Apigenin prevents gamma radiation-induced gastrointestinal damages by modulating inflammatory and apoptotic signalling mediators. Nat Prod Res 2022;36(6):1631–5.
[116] Cai S, Xie LW, Xu JY, et al. (-)-Epigallocatechin-3-Gallate (EGCG) Modulates the Composition of the Gut Microbiota to Protect Against Radiation-Induced Intestinal Injury in Mice. Front Oncol 2022;12:848107.
[117] Yuan X, Long Y, Ji Z, et al. Green Tea Liquid Consumption Alters the Human Intestinal and Oral Microbiome. Mol Nutr Food Res 2018;62(12):e1800178.
[118] Tian T, Zhao Y, Yang Y, et al. The protective role of short-chain fatty acids acting as signal molecules in chemotherapy- or radiation-induced intestinal inflammation. Am J Cancer Res 2020;10(11):3508–31.
[119] Hiippala K, Jouhten H, Ronkainen A, et al. The potential of gut commensals in reinforcing intestinal barrier function and alleviating inflammation. Nutrients 2018;10(8):988.
[120] Chang Pv, Hao L, Offermanns S, Medzhitov R. The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proc Natl Acad Sci U S A 2014;111(6):2247–52.