Prevention of oral mucositis in head & neck cancer patients: A systematic review

Thesis submitted in partial fulfilment for the Masters of Philosophy (Clinical Science)

THE UNIVERSITY OF ADELAIDE

School of Population Health and Clinical Practice

Discipline of Nursing

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August 2012

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Exegesis

Oral mucositis is a common and costly consequence of cancer treatment that currently lacks adequate intervention options. Patients treated for head and neck malignancies are at particularly high risk of severe mucositis, which significantly impedes delivery of therapy and consequently results in poorer outcomes in this population. As such, the quantitative objective of this review was to identify the effectiveness of agents and devices for oral mucositis prevention in newly diagnosed adult head & neck cancer patients being treated with radiotherapy with or without chemotherapy. The methodological framework developed by the Joanna Briggs Institute was followed to conduct the review. The quantitative component of the review considered any randomised controlled trials. In the absence of RCTs other research designs, such as non-randomised controlled trials and before and after studies, were considered for inclusion in a narrative summary to enable the identification of current best evidence. Databases were searched for published and non-published studies. A total of 202 studies were retrieved for review, with 81 studies excluded after reading the full article for clearly not meeting the inclusion criteria of the review. Two reviewers independently assessed 123 studies for methodological quality, excluding 51 for a range of reasons including failure to present baseline data, and use of intervention for mucositis treatment rather than prophylaxis. In the final 72 studies, 13 interventions provided sufficient evidence to be combined in meta-analyses. Only 8 interventions provided weak evidence of benefit to prevent oral mucositis in head and neck cancer patients treated with radiotherapy, with or without chemotherapy, including amifsotine (intravenous administration), aloe vera, G-CSF, honey, sucralfate, morning radiotherapy, providone-iodine and Wobe-Mugos E. Honey was the only intervention to significantly reduce severe mucositis during radiotherapy in all studies, indicating that this is a promising agent deserving further investigation. The remaining interventions had either too few studies conducted or conflicting results to make conclusions regarding effectiveness. A lack of studies which examined the same intervention and inconsistency in reporting of outcomes prevented

aggregation of study results into statistical meta-analysis for most interventions. Furthermore, a general need for additional well designed, adequately powered studies of interventions contributed to the lack of evidence. Future mucositis intervention studies require appropriate placebo controls and double blinding to increase the level of evidence available for the few promising interventions identified.

Declaration

I declare that this thesis is a record of original work and contains no material which has been accepted for the award of any other academic degree or diploma in any university or other tertiary institution, and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Dr Joanne Bowen

Acknowledgements

I would like to thank my supervisors Dr Craig Lockwood and Emeritus Professor Judy Lumby for their expert guidance during preparation of this thesis and throughout my candidature.

I also acknowledge the generous support of the National Health and Medical Research Council funding received during my candidature.

Finally, I would like to acknowledge the invaluable support received from The University of Adelaide and Joanna Briggs Institute Staff.

Chapter 1. Introduction

1.1 Context of the review

Oral mucositis is a common and costly consequence of cancer treatment. It generally manifests as pain, inflammation and loss of mucosal integrity in the oral cavity, oropharynx and hypopharynx (also known as the laryngopharynx), and is associated with significant patient morbidity.[1] Consequences associated with oral mucositis include pain requiring opioid analgesics, impaired oral intake and swallowing requiring feeding tube placement, and infections (viral, fungal and bacterial).[2] Mucositis also increases the risk of potentially fatal septicaemia, as oral ulceration provides an easy portal of entry for microbes in immunosuppressed patients.[3]

Oral mucositis is generally under-reported in clinical trials of anti-cancer agents, since toxicity is a secondary outcome. There is a large difference in the reported frequency of oral mucositis when toxicities are reported incidentally compared to when oral mucositis as a toxicity is the primary outcome. For example, in head and neck cancer treatment, oral mucositis is reported as a toxicity with frequency of 65%, whereas mucositis as an outcome is reported at a frequency of 85%.[4] In addition, clinical trials commonly only report severe toxicity. The incidence of lower grade toxicity, which occurs much more frequently, is often not reported at all. As such, the true burden of mucositis is difficult to estimate. With this in mind, the currently accepted incidence of all grade oral mucositis in cancer patients undergoing treatment with radiotherapy, chemotherapy, or combined chemoradiation ranges from 37% to 100%, depending on the setting.[5-7] The settings with the highest incidence of oral mucositis are head and neck cancer therapy and haematological stem cell transplant.

Significant interest in mucositis from both academic and industry avenues has ensured that there is a wealth of information available on both pathogenesis and management of oral mucositis. This thesis will cover in part the available evidence for oral mucositis management in the specific

context of head and neck cancer treatment, and provide meta-analysis of evidence of effectiveness of interventions.

CLINICAL AND ECONOMIC IMPLICATIONS OF MUCOSITIS

In terms of delivering optimal cancer therapy, oral mucositis presents a unique challenge. Severe mucositis often necessitates dose reduction in subsequent cycles, unplanned treatment interruptions to radiotherapy, alterations to protocols, and occasionally treatment cessation.[8] Long term effects of mucositis-induced treatment interruption and dose reduction on survival have gained relatively little attention. However, it has been well documented that unscheduled radiation treatment breaks have serious consequences for tumour repopulation and local tumour control.[9] Treatment breaks may necessitate larger total doses of radiation to provide adequate tumour control, or the addition of chemotherapy, which has implications for additive or synergistic affects on toxicity. In addition, a study investigating patients with lymphoid malignancies undergoing autologous stem cell transplantation found that severe mucositis was associated with inferior overall survival.[10] Severe mucositis was also found to be a significant risk factor of all cause mortality, with authors recommending that future mucositis prevention studies include relapse and survival endpoints.[10] Importantly, the presence of any grade of oral mucositis significantly reduces quality of life for patients, impacting on function (eating, speaking and swallowing) in addition to pain and other associated complications.[11]

Oral mucositis is expensive for the patient and the health care system. A study quantifying the clinical and economic burden of disease associated with oral mucositis in head and neck cancer patients found that the presence of mucositis increases the cost of care by thousands, and is proportional to severity.[6] This finding has been mirrored in studies conducted in patients with either lung or head and neck cancer [12], and haematological cancers receiving haematological stem cell transplant.[13] It has been found that the incremental oral mucositis cost per-patient exceeds $17,000USD, with increased in-patient hospitalisation being the most significant

contributor.[12] Additional drivers of mucositis-related costs include the increased need for medications, tests, procedures, and clinic visits. As such there is the potential for considerable economic value in effective management of oral mucositis.

MUCOSITIS RISK FACTORS

The risk of oral mucositis varies dependent on the type of tumour, patient characteristics and the treatment administered. The choice of drug (not all agents are equivalently mucotoxic), schedule, and dose-intensity of the treatment will all impact on the risk of toxicity. Patient related variables include age, gender, ethnicity and presence of co-morbidities such as diabetes mellitus, although the absolute association is far less clear for these variables compared to treatment.[14, 15] It is also now appreciated that underlying genetic influences can profoundly affect toxicity. The most widely accepted evidence for the genetic basis of mucositis risk is the observation that patients deficient in certain drug-metabolising enzymes are at a higher risk of treatment toxicity. Specific examples of these include deficiencies in UDP glucuronosyltransferase (UGT), thymidylate synthase (TS) and dihydropyrimidine dehydrogenase (DPYD), relevant to irinotecan, methotrexate and 5-FU treatment respectively.[16, 17]

HEAD AND NECK CANCER PATIENTS

Patients with head and neck neoplasms are particularly at risk of oral mucositis. Head and neck cancers make up a diverse group of tumours which can arise in numerous structures including, lips, salivary glands, sinuses, the oral cavity, pharynx or larynx. Head and neck squamous cell carcinoma (HNSCC) comprises 90-95% of all tumours in this group and is currently the 6th most common neoplasm in the world.[18] Treatment varies depending on the site, grade and stage of the primary tumour, as well as the patient's age and general medical condition. Methods include surgery, radiotherapy, chemotherapy and combinations of these.[19] Two thirds of patients present with locally advanced tumours and are treated either post-operatively or definitively with

intensive chemoradiotherapy (including 70 Gy + cisplatin-based chemotherapy), which is responsible for severe acute and late toxicities.[19] It has been estimated that 80-100 percent of patients treated by this regimen suffer oral mucositis to some degree [20], however the rate and severity vary as a function of the radiation dose, fractionation, and the field involved.[21] In general, larger fields and higher radiation doses, as well as hyperfractionation and accelerated fractionation schedules tend to result in increased rates of severe oral mucositis.[22] Chemotherapy further sensitises the mucosa to radiotherapy, as shown by the higher incidence of severe oral mucositis in head and neck cancer patients treated with concurrent chemoradiotherapy compared to radiotherapy alone.[23] Finally, the introduction of new molecularly targeted agents for the treatment of head and neck cancers such as the monoclonal antibody, cetuximab, has added further complexity to the presentation of oral mucosal injury.[24, 25]

HEAD AND NECK CANCER TREATMENT

Head and neck cancer treatment has evolved greatly over the last two decades. Whilst conventional radiotherapy has remained a mainstay in the treatment of patients with early disease [26], in patients with locally or regionally advanced tumours, altered fractionation, conformal radiation, and the addition of combination therapies has changed the face of treatment.

Attempted improvement of locoregional tumour control with altered fractionation has been investigated widely. Accelerated fractionation (AF) reduces overall treatment time with or without total dose reduction, and hyperfractionation (HF) delivers higher total dose by small multi-daily radiation doses.[27] A meta-analysis of studies comparing conventional radiotherapy to HF or AF in patients with non-metastatic head and neck cancer found that both HF and AF confer a significant survival benefit.[28] HF was found to provide the highest locoregional tumour control and survival advantage.

More recently, addition of chemotherapy for improvement of locoregional control has shown some benefit, although with increased toxicity.[29] Chemotherapy can be administered before, at the same time, or after locoregional (radiation +/- surgery) treatment. This corresponds to induction, concomitant or adjuvant therapy, respectively. A recent meta-analysis of chemotherapy in non-metastatic head and neck squamous cell carcinoma treatment found that concomitant chemotherapy with radiation gave the highest survival benefit, in comparison to induction and adjuvant chemotherapy.[30] In regards to the most effective chemotherapeutic agents, cisplatin alone, cisplatin or carboplatin associated with 5-FU, or other poly-chemotherapy including either a platin or 5-FU showed similar benefit. Interestingly, the advantage of concomitant chemotherapy was maintained for both conventional and altered fractionation radiotherapy.[30] Due to the improvements in overall survival and locoregional control for all tumour types, combined chemoradiation is the current choice for treatment of high risk patients with locally advanced head and neck cancer.[31] Finally, addition of a radiosensitiser, such as cetuximab, during treatment of advanced or metastatic head and neck cancer is currently under intensive study.[32] Initial survival outcomes have been promising [33], although whether this approach also increases the risk of oral toxicity is still to be fully evaluated.[34] An overview of the therapeutic index for current strategies in head and neck cancer treatment is shown in figure 1.

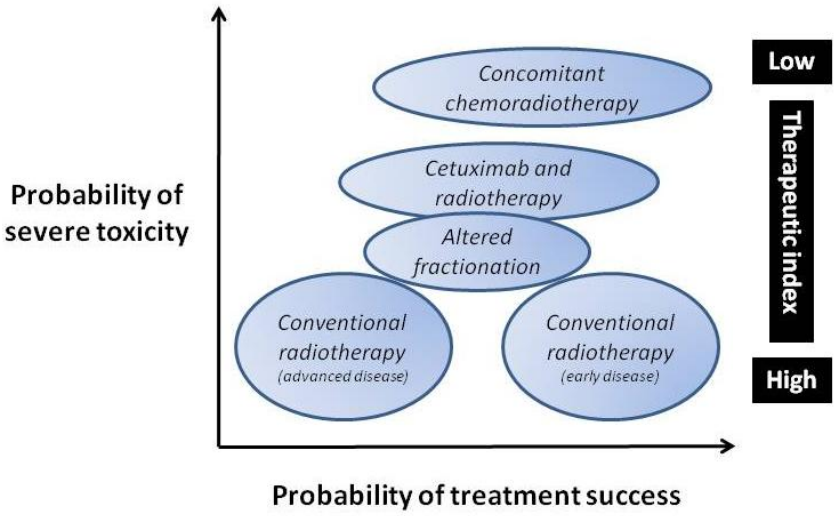

Figure 1. Therapeutic index of strategies used to treat head and neck cancer. Altered fractionation and concomitant chemoradiotherapy are associated with improved locoregional control and survival, although carry an increased risk of toxicity. These approaches have been developed to improve outcomes in patients with locally advanced disease treated with radiotherapy.

RELATIONSHIP BETWEEN PATHOBIOLOGY AND INTERVENTIONS

As with other treatment-related toxicities, oral mucositis occurs in response to the damaging effects of cytotoxic drugs and radiation on normal tissue.[35] The current understanding of mucositis pathobiology includes a multiphase process which describes pan tissue changes along the length of the alimentary canal.[36] In an oversimplification, the initiating event finds cytotoxic agents inducing damage through the generation of reactive oxygen species which causes both direct damage to tissue components of the mucosa and activation of secondary signalling. The following phase centres around message generation, primarily through activation of the transcription factor, NFkappaB, which leads to the upregulation of many genes involved in perpetuating mucosal injury, including proinflammatory cytokines, adhesion molecules, and cyclooxygenase-2. A feedback loop is then set up, whereby the proinflammatory cytokine, TNFalpha, acts on a number of pathways to reinforce NFkappaB activation and the pro-apoptotic

ceramide pathway. The most clinically significant phase of the process occurs with loss of epithelial integrity and bacterial colonisation, which leads to subsequent further proinflammatory cytokine production. It is theorised that patients with genetic profiles that predict enhanced cytokine responses are at increased risk of severe mucosal injury.[37] Mucositis is usually self-resolving once treatment ceases, with healing occurring through renewal of epithelial proliferation and differentiation and reestablishment of the normal local microbial flora to the mucosal surface.[37] The orodigestive mucosa appears to be one of the most sensitive tissues to the effects of chemotherapy and radiotherapy, however, it is likely that all mucosal surfaces are affected to some degree.[38]

Improved knowledge of the mechanistic underpinnings of treatment-induced mucositis has streamlined development of intervention strategies targeting biological changes involved in the phases responsible for development and healing of ulceration. Although progress is being achieved, there is still much to be learned about this complex problem.

MUCOSITIS MANAGEMENT

Among treatment centres there is a plethora of approaches to prevention and treatment of oral mucositis.[39] "Magic" mouthwash through to low energy lasers may be routinely used depending on the country and institution as there is currently no standardised approach employed worldwide. This is most likely due to the vast number of studies investigating oral mucositis conducted over the past three decades, which often give conflicting or very low evidence of benefit, and the inadequate implementation of guidelines which are available.[40] The number of agents or devices investigated, under development or being patented for prevention of mucositis is huge and constantly increasing. However, there are but a handful of recommended practices for the prevention and treatment of oral mucositis, and to date, the only drug approved by the FDA for prevention of oral mucositis is palifermin [Kepivance® Biovitrum], which is indicated in

patients undergoing myelotoxic therapy associated with hematopoietic stem-cell transplantation.[41]

DIAGNOSIS OF ORAL MUCOSITIS

To diagnose the presence of mucositis, and evaluate the effectiveness of a mucositis intervention under study, a number of oral mucositis assessment tools are available (the most commonly used are summarised in table 1). These may be physician administered, patient reported, or a combination of both, and describe functional impairment (functional/subjective changes) with or without tissue changes including ulceration and erythema (physical/objective changes). A summary of scales developed to investigate oral changes both in research and clinical trials is included in an excellent review by Eilers and Epstein (2004).[42] To date, no one assessment scale has been universally accepted, leading to varied use and combinations of tools implemented across studies. The inconsistencies between instruments are a major limitation when assessing evidence of effectiveness of mucositis interventions across different studies. Guidelines for assessment of mucositis in adult patients are also available.[43] It is strongly recommended that oral mucositis should be assessed using a standardised protocol for effective patient management. In addition, routine assessments should take place frequently, with patient self-reporting forming an integral part of the assessment.

Table 1. Commonly used oral mucositis assessment scales in head and neck cancer treatment

Instrument	Description			
	1	2	3	4
WHO	Soreness with or without erythema	Erythema, ulcers, can eat solids	Ulcers, liquid diet only	Alimentation not possible
NCI CTC v2.0 (for radiotherapy)	Erythema	Patchy pseudomembranous reaction < 1.5 cm, noncontiguous	Confluent pseudomembranous reaction >1.5 cm, contiguous	Necrosis or deep ulceration with or without bleeding
NCI CTCAE v3.0 (clinical criteria)	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis, significant spontaneous bleeding; life-threatening consequences
(functional criteria)	Minimal symptoms, normal diet	Symptomatic but can eat and swallow modified diet	Symptomatic and unable to adequately aliment or hydrate orally	Symptoms associated with life-threatening consequences
RTOG	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosanguinitis discharge, may experience moderate pain requiring analgesia	Confluent fibrinous mucositis, may include severe pain requiring narcotic	Ulceration, haemorrhage or necrosis
WCCNR	Slight erythema, 1-4 ulcers, no bleeding, oral sensitivity, mild discomfort	Moderate erythema, >4 ulcers, tolerates soft bland diet, use of analgesics for moderate pain	Severe erythema, >1 confluent ulcer, spontaneous bleeding, alimentation not possible, severe pain requiring systemic analgesics	N/A
OMAS	lesion < $1cm^2$,	lesion of $1cm^2$ to $3cm^2$,	Lesion greater than $3cm^2$	N/A
Ulceration				
Erythema	not severe	severe	N/A	N/A

*WHO = World Health Organization; NCI CTC = National Cancer Institute Common Toxicity Criteria, RTOG = Radiation Therapy Oncology Group; CTCAE = Common Terminology Criteria for Adverse Events; WCCNR = Western Consortium for Cancer Nursing Research, OMAS = Oral Mucositis Assessment Scale. Adapted table

*Data for table compiled from the following websites: www.kepivance.com/nurses/assessment.jsp , www.kepivance.com/oral_mucositis/assessment.jsp , www.eortc.be/services/doc/ctc/ctcv20_4-30-992.pdf (accessed12/12/2011)

CURRENT STATE OF EVIDENCE

As a recognised area of need, the Joanna Briggs Institute reviewed articles describing interventions for prevention and treatment of oral mucositis induced by radiotherapy and chemotherapy.[44] The findings of that systematic review lead to the publication in 1998 of one of the first clinical practice guidelines, which recommended that all patients at risk of mucositis receive a standardised oral care regime.[45] This oral care protocol, as an ongoing part of care, is aimed at ensuring patients maintain a clean mouth to limit opportunistic infection, and has been repeatedly endorsed in subsequent guidelines. The Cochrane Oral Health Group of the Cochrane Collaboration has followed with their own series of systematic reviews (with 3-yearly updates) in the field, finding a number of interventions which show varying levels of effectiveness.[46-55] The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (the peak professional body in supportive cancer care) has also conducted systematic reviews of the literature and published their own set of guidelines.[56, 57] The 2007-published Clinical Practice Guidelines for the Prevention and Treatment of Mucositis, an update from the originally published guidelines in 2004, could only offer four recommendations for the prevention of oral mucositis in head and neck cancer patients, and of these just two were positive. The approaches recommended for prevention of oral mucositis are 1) benzydiamine hydrochloride, and 2) midline radiation blocks and 3-dimensional radiation treatment. Benzydamine hydrochloride is an agent with anti-inflammatory, analgesic, anaesthetic, and antimicrobial properties. Anti-inflammatory effects, including inhibition of pro-inflammatory cytokines such as TNFalpha, are thought to be the main mode of action. It appears to be effective for prevention of oral mucositis in patients receiving moderate dose radiotherapy.[58] Radiation blocks and 3-dimensional treatment limits normal tissue volume falling with the treatment field, sparing healthy mucosa from damaging radiation.[22] The two negative recommendations (a recommendation not to use agents for the prevention of oral mucositis) were for 1) chlorhexidine, and 2) antimicrobial lozenges. Despite infection being considered an important component of the pathobiology of

oral mucositis, chlorhexidine, with its broad spectrum antiseptic properties, and lozenges containing a mixture of antimicrobials were unable to show any benefit for mucositis incidence or severity. The European Society of Medical Oncology (ESMO) is the latest organisation to publish guidelines for the management of mucositis, using the findings of the MASCC systematic review to help broaden impact.[59-61] Despite the world-wide efforts to reduce the burden of cancer therapy-induced mucositis, it remains a problem requiring further high quality research and utilisation of the available evidence to improve outcomes.

1.2 Scope of review

The authors of the systematic reviews conducted by the Joanna Briggs Institute, Cochrane Collaboration and Mucositis Study Group of MASCC all agreed that a lack of high quality, well designed, adequately powered trials published, limited the ability to make conclusions regarding the effectiveness of the interventions studied. As such, the proposed systematic review aims to compile the evidence testing interventions for prevention (and not palliation) of oral mucositis in head and neck cancer patients with the objective to provide a comprehensive overview of the research conducted in the last decade. It is expected that thelatest primary research publications will provide a great deal of valuable information, andthis will be considered in context with the evidence available within previously completed systematic reviews. Finally, there has been more than 10 years since JBI methodology was last used to assess effectiveness of interventions for oral mucositis. This systematic review will provide an update on the state of knowledge through consistent application of JBI methodology.

Two previous systematic reviews in particular have helped form this approach.[62, 63] Sutherland et al (2001) searched the databases, Medline, CINAHL, Embase and Cancerlit, for published and unpublished studies between 1966 and 2000 describing interventions for prevention of oral mucositis in head and neck patients receiving radiotherapy with or without chemotherapy. In

addition to randomised controlled trials (RCTs), phase II and descriptive studies were also reviewed, although these were not included in meta-analyses. Trials were assessed for methodological quality using the method of Jadad et al (1996).[64] This utilises a validated instrument which scores study quality based on presence/absence of randomisation, blinding and reporting of participant withdrawals. The primary outcome measure of interest was the proportion of patients developing "severe oral mucositis", which was defined as the cut point in the assessment scale used that separated patients from having none, some or moderate oral mucositis, to patients with severe or very severe oral mucositis. When the cut point of the scale was unclear, the authors used the review by Parulekar et al (1998) as a guide.[65] A total of 13 RCTs were included in the meta-analysis of severe mucositis, which covered the interventions; sucralfate, beta carotene, prostaglandin, hydrogen peroxide, low level laser therapy, benzydamine, chlorhexidine, povidone iodine and PTA lozenge (polymyxin E, tobramycine, and amphotericin B). The authors found an odds ratio (OR) of 0.64 (95% CI: 0.46-0.88) in favour of intervention when all agents were considered together. However, there was equivocal evidence of benefit for the individual agents, and only chlorhexidine, sucralfate and PTA lozenge had more than one study included in the analysis. Stokman et al (2006) searched Medline, CINAHL and Embase for published RCTs between 1966 and 2004 describing prophylactic interventions for oral mucositis in head and neck cancer patients treated with either radiotherapy, chemotherapy, or combined chemoradiation.[62] Where more than one study that fulfilled the inclusion criteria per intervention was available, it was included in the meta-analyses, giving a total of 45 studies covering 8 interventions; oral cooling, GM-CSF/G-CSF, amifostine, chlorhexidine, iseganan, glutamine, sucralfate and PTA. Interventions found to have an OR in favour of treatment included PTA, systemic GM-CSF/G-CSF, oral cooling and amifostine. Although the authors found 27 different mucositis intervention agents, only a few agents could be combined in statistical meta-analyeses. The reasons for this included only single studies being available for multiple

interventions, and the need to exclude studies based on poor study design. The authors commented that this limited the number of statistically supported conclusions being possible.

1.3 Justification of review approach

I have chosen to conduct a systematic review with meta-analysis of effectiveness of interventions for oral mucositis in head and neck cancer patients. This approach to evaluating research literature has become increasingly popular over the last decade as evidence-based health care has evolved. Evidence-based healthcare is the integration of best research evidence with clinical expertise and patient values [66], which aids in best practice, ultimately improving patient care. Systematic reviews contribute to this process by secondary research synthesis of multiple studies, enabling increased access to evidence delivered in an efficient manner.[67]

Systematic reviews aim to avoid bias when evaluating the evidence, and have a number of benefits to the traditional narrative literature review. Narrative reviews generally do not describe the process of searching the literature, article selection, or study quality assessment. Following summary of the included articles, inferences are often made, although these are not necessarily evidence-based. As such, narrative reviews are susceptible to bias if a comprehensive literature search is not performed, or if the data is selected to convey the author's views on the described topic.[68] In contrast, systematic reviews a priori set defined clinical questions, methodological approach for inclusion and evaluation of literature, and select the most important research outcomes to extract. When appropriate, the outcome data are pooled and statistically analysed (meta-analysis). Therefore inferences made from systematic reviews can be considered evidence-based.

1.4 Assumptions and limitations of approach

Due to the expected rigor when conducting a systematic review and meta-analysis of interventions, evidence in this form sits atop the evidence hierarchy.[69] However, the assumption is that the review is of high quality itself, and that the meta-analysis has been conducted only when statistically appropriate.[67] An assessment of methodology used in systematic reviews and guideline development for prevention and treatment of oral mucositis found that indeed the quality varied greatly among the 30 items evaluated.[70] In fact, using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument to evaluate guidelines (The AGREE Collaboration. Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument. www.agreecollaboration.org) and the Overview Quality Assessment Questionnaire (OQAQ) for evaluation of systematic reviews [71], the authors found that the quality of the majority of these documents was low.

To single out just one study is unfair, however, a comment in Evidence Based Dentistry highlighted the fact that a low quality systematic review may not go un-noticed.[72] When commenting on the systematic review and meta-analyses conducted by Stokman et al (2006) for the prevention of oral mucositis, Dr Richards noted that the Cochrane Library was not utilised in the search strategy, nor were the Cochrane reviews on the same topic mentioned. Another point of concern was the exclusion of articles written in languages other than English. Unfortunately, this aspect of reviewing the literature is a difficult one to overcome, and a flaw that will also be present in my review thesis. A further limitation is the relative difficulty in including non-published studies. Despite the availability of excellent databases to locate studies not yet completed, or presented in abstract form only, the necessity (and mostly failure) for responses from authors and study co-ordinators to provide additional information is a barrier to inclusion. As such, the bias for published studies continues to be present. Overall, attempts have been made to ensure methodological flaws are kept to a minimum in this systematic review, but I acknowledge that some are present.

Chapter 2. Systematic review protocol

The systematic review described within this thesis follows the methodological framework developed by the Joanna Briggs Institute. Details specific to the review topic are explained below.

2.1 Statement of review question

What is the level of evidence for effectiveness of agents and devices for oral mucositis prevention in newly diagnosed adult head & neck cancer patients being treated with radiotherapy with or without chemotherapy?

2.2 Objectives of review

The objectives of this review were to determine the effectiveness of oral mucositis interventions on incidence and severity of mucositis and selected complications in patients with locally advanced and/or metastatic head and neck squamous cell carcinoma treated with radiotherapy or chemoradiotherapy. The findings will be used to support current clinical practice guidelines and to inform future studies where a guideline is not currently possible.

2.3 Inclusion criteria

2.3.1 Types of studies

This review considered any randomised controlled trials; in the absence of RCTs other research designs, such as non-randomised controlled trials and before and after studies, were considered for inclusion in a narrative summary to enable the identification of current best evidence regarding evidence for prevention of oral mucositis in head and neck cancer patients. Systematic reviews were excluded from data extraction, however were considered during the discussion of results and also cross-checked for missing studies.

2.3.2 Types of participants

The review considered studies that included adult cancer patients (>18 years) enrolled through tertiary cancer centres treated as in-patients or out-patients.

Participants were adults with biopsy proven squamous cell carcinoma of the head and neck region, with locally advanced and/or metastatic disease, not previously treated with chemotherapy or radiotherapy. Patients were treated with conventional, accelerated or hyperfractionated radiotherapy. In addition, concomitant, neoadjuvant or induction chemotherapy could be included in the treatment regimen.

2.3.3 Types of interventions

The review considered studies that evaluated agents, devices and techniques which aimed specifically to prevent the incidence or reduce the severity of oral mucositis. This included, but was not limited to; barriers, growth factors, low level laser therapy, pharmalogicals, changes in delivery of conventional treatment and oral care practices. Papers investigating interventions not administered in a measured/controlled way or without standardised components were excluded from the review.

2.3.4 Types of comparisons

Comparators included placebo, best possible care standard of the hospital (eg. oral care regime), other active treatments, oral rinsing agents (commonly sterile water or saline), or nothing, depending on the study.

2.3.5 Types of outcome measures

This review considered studies that included the following outcome measures:

Primary outcomes; incidence of oral mucositis, incidence of severe mucositis.

Mucositis as an outcome was dichotomised to 0 vs 1+ (absent vs present) in the first analysis, and, 0-2 vs 3+ (moderate vs severe) in the second analysis.

Secondary outcomes; severity of mucositis (mean ± SD, scale score), severity of pain (mean ± SD, Visual Analogue Scale score) unplanned radiation treatment breaks (number each group), dose reductions (number each group), non-prophylactic placement of feeding tube (number each group)

Mucositis severity is scored using the five point WHO or NCI-like scales (ranging from 0 (normal) to 4 (very severe)) in the overwhelming majority of clinical trials.[15] As such, results from studies using these methods were included in the meta-analysis, and studies using other scales were described in narrative form only when included. If weekly oral mucositis incidence or severity data was presented rather than cumulative incidence or average severity, the week 6 or 7 (whichever was the latest) data was used for extraction. Oral mucositis severity increases as the dose of radiation increases, as such it is necessary to take the scores from the last week of therapy.

2.4 Review methods

2.4.1 Search strategy

The search strategy aimed to find both published and unpublished studies reported from 1st June 1998 to 1st June 2010. A three-step search strategy was utilised in this review. An initial limited search of PubMed/MEDLINE for articles published in the previous 12 months was undertaken (shown below) followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using identified keywords and index terms combined into a complete search strategy was then undertaken across all included databases. Thirdly, the reference list of included articles was searched for additional studies.

The databases searched include:

Published literature: Scopus, PubMed/MEDLINE (complete search strategy Appendix 3a), EMBASE (complete search strategy Appendix 3b), CINAHL (complete search strategy Appendix 3c), Cochrane Library (CENTRAL) (complete search strategy Appendix 3d), ISI Web of Science (complete search strategy Appendix 3e), EBM Reviews, Clinical Trials.gov, Clinical Evidence, Current Controlled Trials, BioMed Central, ACP Journal Club, ASCO abstracts, Informit,

Unpublished/Grey literature: Mednar, Google Scholar, Australasian Digital Thesis Catalogue.

The initial limited search strategy was conducted as follows, with keywords and index terms identified listed in table 2.

PubMed line request: (mucositis [mh] AND head and neck neoplasms [mh]) AND (Therapy/Broad[filter]) AND (2009/06:2010/06 [dp])

Search Details: ("mucositis"[MeSH Terms] AND "head and neck neoplasms"[MeSH Terms]) AND Therapy/Broad[filter] AND (2009/06[PDAT] : 2010/06[PDAT])

Clinical Queries using Research Methodology Filter:

therapy, broad = ((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])

Table 2. Terms combined to generate complete database search strategies

Mucositis	**Head and neck neoplasms**	**Cancer and variants**	**Locations**	**Methods**	**Subheadings**	**Treatment**
Mucositis Stomatitis Mucositides Stomatitides Mucosal injur* Mucosal barrier Mucosa inflammation Mucous membrane	Head and neck neoplasms	Neoplasm* Cancer Tumour* Tumor* Malignanc* Carcinoma*	Mouth Pharynx Nasal cavity Nasopharynx Oropharynx Laryngopharynx Hypopharynx	Randomized controlled trial Controlled clinical trial Random allocation Double-blind method Single-blind method Clinical trial* Research design Comparative study Evaluation studies as topic Follow-up studies Prospective stud* Cross over stud*	Radiation/adverse effects Drug therapy/adverse effects	Chemotherap* Radiat* Radiother* Irradiat* Cisplatin Fluorouracil Cetuximab Carboplatin Paclitaxel

2.4.2 Assessment of methodological quality

Papers selected for retrieval were assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardised critical appraisal instruments for RCTs from the Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix 1). Any disagreements that arose between the reviewers were resolved through discussion, or with a third reviewer. Papers were required to receive a minimum 50% yes scores in MAStARI criteria checklist for inclusion. Furthermore, certain criteria are weighted and considered vital for inclusion, specifically criteria 7, 8 and 9 in the MAStARI checklist.

2.4.3 Data extraction

Data was extracted from papers included in the review using the standardised data extraction tool from JBI-MAStARI (Appendix 2). The data extracted included specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

2.4.4 Data synthesis

Papers were, where possible, pooled in statistical meta-analysis using JBI-MAStARI, with results displayed in a Forest Plot. All results were subject to double data entry. Risk ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals (CI) were calculated for analysis using a fixed effects model (Mantel Haenszel). Heterogeneity was assessed using Chi-square test. When the included studies showed heterogeneity regarding the effect estimates with a *P* value of less than 0.05, the random-effects model was used. Where statistical pooling was not possible, the findings are presented in narrative form.

Chapter 3. Results

3.1. Description of studies

The database searches found a total of 2464 studies. After removal of duplicates and irrelevant studies based on the title and abstract, 202 were retrieved for detailed analysis. A further 79 studies were removed after reading the full article. Finally, 123 studies underwent appraisal. Only 72 studies were included in the final review, which included 6027 participants testing 48 interventions in total (summarised in Appendix 4). The workflow is shown in figure 2. Studies were excluded for a mixture of reasons, briefly including; failure to present data for mucositis, poorly reported and at high risk of bias, groups not comparable at baseline, intervention administered therapeutically rather than prophylactically, not primary studies, study reported previously in another journal, and literature reviews (see list of excluded studies for further information, Appendix 5).

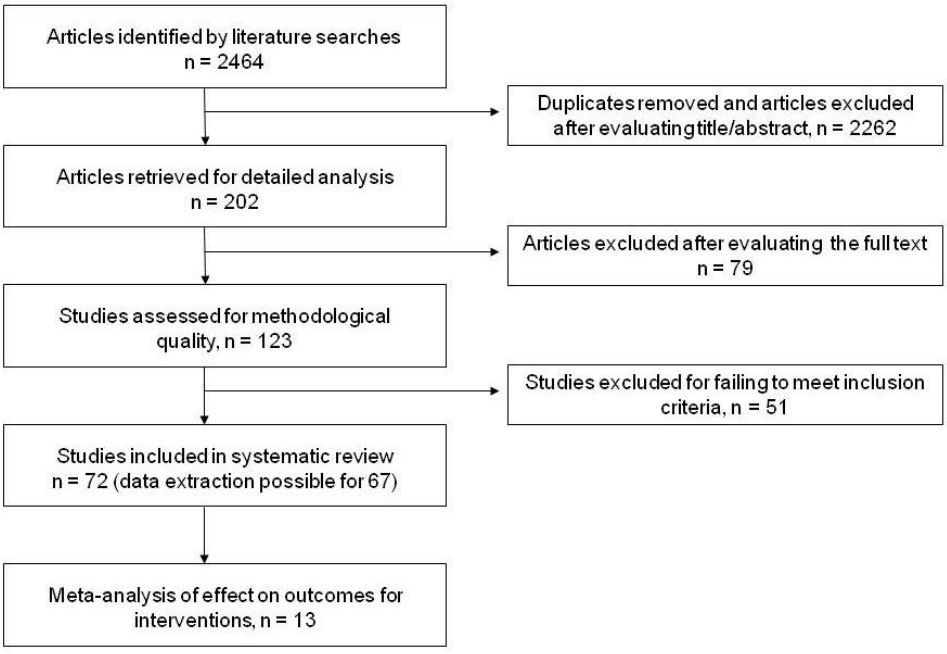

Figure 2. Systematic review workflow.

The included studies were of the following methodological designs: Cohort/Case Control (1)[73], Case studies (4)[74-77], RCTs/Psuedo-RCTs (67)[81-142]. Cohort/Case control and case studies were only included when there was a failure to identify evidence of a higher quality for the intervention under study.

The included studies were conducted in 29 countries (UK, Poland, USA, Netherlands, Greece, Germany, France, Turkey, Thailand, Iran, Canada, Hong Kong, India, Israel, Spain, Korea, Argentina, Taiwan, Italy, Austria, Finland, Malaysia, Egypt, Australia, Uruguay, China, Norway Belgium, Brazil), most commonly USA with 11 studies.[74, 76, 78-86] The number of participants included in the studies investigating oral mucositis interventions ranged from 13 patients[87] to 918 patients.[88] Oral mucositis was measured using a range of assessment tools and at different frequencies. Most commonly reported was weekly scoring conducted by the physician using a 5-point scale. Patient evaluations were rarely carried out, and not included in this review.

3.1.1. Summary of interventions of included studies

Table 3. Interventions of included studies

Intervention	Studies
Accelerated radiotherapy vs conventional radiotherapy	Bentzen et al (2001)[88], Wygoda et al (2009)[73]
Amifostine s.c. vs nothing	Anne et al (2007)[74], Braaksma et al (2005)[89], Koukourakis et al (2000)[90]
Amifostine i.v. vs nothing	Antonadou et al (2002)[91], Bennett et al (2001)[92], Bourhis et al (2000)[93], Brizel et al (2000)[79], Buntzel et al (1998)[94], Karacetin et al (2004)[95], Vacha et al (2003)[96], Veerasarn et al (2006)[97]
Amifostine i.v. vs placebo	Buentzel et al (2006)[98]
Allopurinol vs placebo	Abbasi Nazari et al (2007)[99]
Aloe vera vs placebo	Puataweepong et al (2009)[100], Su et al (2004)[84]
BCoG lozenge vs placebo	El-Sayed et al (2002)[101]
Benzydamine vs chlorhexidine	Cheng et al (2006)[102]
Benzydamine vs placebo	Epstein et al (2001)[81], Kazemian et al (2009)[103]
Chlorhexidine vs water	Madan et al (2008)[104]
Cisplatin vs vinorelbine	Sarkar et al (2008)[105]
Dead sea products vs nothing	Matceyevsky et al (2007)[106]
EGF vs placebo	Wu et al (2009)[107]
Flurbiprofen vs nothing	Stokman et al (2005)[77]
Fluconazole (prophylactic) vs	Nicolatou-Galiatis et al (2006)[108]

flconazole (therapeutic)	
G-CSF (s.c) vs nothing	Mascarin et al (1999)[109]
G-CSF (s.c.) vs placebo	Schneider et al (1999)[83], Su et al (2006)[85]
Glutamine i.v. vs placebo	Cerchietti et al (2006)[110]
Glutamine rinse vs saline	Huang et al (2000)[111]
GM-CSF mouthwash vs hydrocortisone	Sprinzl et al (2001)[112]
GM-CSF mouthwash vs sucralfate	Saarilahti et al (2002)113
GM-CSF (s.c.) vs nothing	McAleese et al (2006)[114]
GM-CSF (s.c.) + sucralfate vs sucralfate	Makkonen et al (2000)[115]
Honey vs nothing/saline	Biswal et al (2003)[116], Mottalebnejad et al (2008)[117], Rashad et al (2009)[118]
Indigowood vs saline	You et al (2009)[119]
Iodine vs water	Adamietz et al (1998)[120], Madan et al (2008)[104]
Iseganan vs placebo	Trotti et al (2004)[86]
LLLT vs saline	Arun Maiya et al (2006)[121]
LLLT vs sham laser	Bensadoun et al (1999)[122]
Misoprostol vs nothing	Johnson et al (2002)[76]
Misoprostol vs placebo	Veness et al (2006)[123]
Morning Rx vs afternoon Rx	Bjarnason et al (2009)[124], Goyal et al (2009)
Orgotein	Escrinbano et al (2002)[75]
Palifermin vs placebo	Brizel et al (2008)[78]
Payayor vs benzydamine	Putwatana et al (2009)[125]
Perio-Aid Tratamiento vs placebo	Lanzos et al (2010)[126]
Pilocarpine vs placebo	Scarantino et al (2006)82, Warde et al (2002)127
Prednisone vs placebo	Leborgne et al (1998)[128]
PTA paste vs placebo	Stokman et al (2003)[129], Wijers et al (2001)[130]
QRLYD vs Dobell's solution	Wu et al (2007)[131]
Salt/bicarb rinse vs water	Madan et al (2008)[104]
Selenium vs nothing	Buntzel et al (2010)[132]
Sucralfate vs placebo	Carter et al (1999)[80], Cengiz et al (1999)[133], Emami et al (2008)[134], Etiz et al (2000)[135], Evensen et al (2001)[136], Lievens et al (1998)[137]
Vitamin E vs placebo	Ferreira et al (2004)[138]
WF10 vs nothing	Penpattanagul et al (2007)[87]
Wobe-Mugos vs nothing	Gujral et al (2001)[139], Kaul et al (1999)[140]
Wobe-Mugos vs placebo	Dorr et al (2007)[141]
Zinc vs placebo	Ertekin et al (2004)[142], Lin et al (2006)[143]

3.1.2. Summary of outcomes reported in included studies

Table 4. Outcomes of included studies

Outcome	Studies
Incidence of mucositis	Abbasi Nazari et al (2007)[99], Adamietz et al (1998)[120], Antonadou et al (2002)[91], Arun Maiya et al (2006)[121], Biswal et al (2003)[116], Bourhis et al (2000)[93], Brizel et al (2000)[79], Buentzel et al (2006)[98], Buntzel et al (1998)[94], Buntzel et al (2010)[132], Cengiz et al (1999)[133], Cheng et al (2006)[102], El-Sayed et al (2002)[101], Emami et al (2008)[134], Ertekin et al (2004)[142], Evensen et al (2001)[136], Goyal et al (2009)[144], Gujral et al (2001)[139], Huang et al (2000)[111], Karacetin et al (2004), Kaul et al (1999)[140], Makkonen et al (2000)[115], Matceyevsky et al (2007)[106], McAleese et al (2006)[114], Penpattangul et al (2007)[87], Puataweepong et al (2009)[100], Putwatana et al (2009)[125], Rashad et al (2009)[118], Sarkar et al (2008)[105], Scarantino et al (2006)[82], Stokman et al (2003)[129], Su et al (2006)[85], Trotti et al (2004)[86], Veness et al (2006)[123], Wijers et al (2001)[130], Wu et al (2007)[131], You et al (2009)[119]
Incidence of severe mucositis	Abbasi Nazari et al (2007)[99], Adamietz et al (1998)[120], Anne et al (2007)[74], Antonadou et al (2002)[91], Arun Maiya et al (2006)[121], Bentzen et al (2001)[88], Biswal et al (2003)[116], Bjarnason et al (2009)[124], Bourhis et al (2000)[93], Braaksma et al (2005)[89], Brizel et al (2000)[79], Brizel et al (2008)[78], Buentzel et al (2006)[98], Buntzel et al (1998)[94], Buntzel et al (2010)[132], Carter et al (1999)[80], Cengiz et al (1999)[133], Cerchietti et al (2006)[110], Cheng et al (2006)[102], El-Sayed et al (2002)[101], Emami et al (2008)[134], Ertekin et al (2004)[142], Evensen et al (2001)[136], Ferreira et al (2004)[138], Gujral et al (2001)[139], Huang et al (2000)[111], Johnson et al (2002)[76], Karacetin et al (2004)[95], Kazemian et al (2009)[103], Kaul et al (1999)[140], Koukourakis et al (2000)[90], Lin et al (2006)[143], Mascarin et al (1999)[109], Matceyevsky et al (2007)[106], Mcaleese et al (2006)[114], Nicolatou-Galiatis 2006, Puataweepong et al (2009)[100], Rashad et al (2009)[118], Sarkar et al (2008)[105], Scarantino et al (2006)[82], Schneider et al (1999)[83], Sprinzl et al (2001)[112], Su et al (2004)[84], Su et al (2006)[85], Trotti et al (2004)[86], Veerasarn et al (2006)[97], Veness et al (2006)[123], Warde et al (2002)[127], Wijers et al (2001)[130], Wu et al (2009)[107], Wu et al (2007)[131], Wygoda et al (2009)[73], You et al (2009)[119]
Radiation treatment interruptions	Antonadou et al (2002)[91], Biswal et al (2003)[116], Brizel et al (2008)[78], El-Sayed et al (2002)[101], Epstein et al (2001)[81], Ertekin et al (2004)[142], Etiz et al (2000)[135], Koukourakis et al (2000)[90], Leborgne 1998, Mascarin et al (1999)[109], Matceyevsky et al (2007)[106], Nicolatou-Galiatis 2006, Penpattanagul et al (2007)[87], Puataweepong et al (2009)[100], Putwatana et al (2009)[125], Rashad et al (2009)[118]
Severity of mucositis	Arun Maiya et al (2006)[121], Bensadoun 1999, El-Sayed et al (2002)[101], Emami et al (2008)[134], Etiz et al (2000)[135], Gujral et al (2001)[139], Huang et al (2000)[111], Madan et al (2008)[104], Mascarin et al (1999)[109], Putwatana et al (2009)[125], Stokman et al (2005)[77]
Feeding tube placement	Bourhis et al (2000)[93], Braaksma et al (2005)[89], Carter et al (1999)[80], Cerchietti et al (2006)[110], Epstein et al (2001)[81], Rashad et al (2009)[118], Saarilahti et al (2002)[113], Stokman et al (2003)[129], Warde et al (2002)[127]
Severity of pain	Arun Maiya et al (2006)[121], Putwatana et al (2009)[125], Stokman et al (2005)[77], Veness et al (2006)[123]

3.2 Review findings

3.2.1 Accelerated radiotherapy

Two studies with a total of 984 participants investigated the relationship between radiotherapy scheduling and mucosal toxicity (Figure 3).[73, 88] Since radiation dose and frequency is known to be a risk factor in severity of mucositis, it is not surprising that researchers have looked to evaluate the benefit of potential increased tumour response against certain increased toxicity.

Bentzen et al (2001) analysed toxicity data from the randomised controlled trial of CHART (continuous hyperfractionated accelerated radiotherapy) vs. conventional radiotherapy in head and neck cancer.[88] The trial accrued 918 patients from March 1990 to April 1995 with a 3:2 allocation favouring CHART. Conventional RT consisted of 66 Gy delivered as 2 Gy per fraction, 1 fraction per day, 5 days a week. Accelerated RT consisted of 1.5 Gy per fraction, 3 fractions a day, on 12 consecutive days including the weekend to a total dose of 54 Gy. Mucositis was evaluated weekly for 8 weeks after the start of treatment using a study-specific three point grading scale similar to NCI CTC v2/RTOG (0: None, 1: (not used), 2: Patchy, 3: Confluent). The analysis found that the incidence and peak prevalence of confluent mucositis was higher after CHART than after conventional radiotherapy. Therefore, the average time spent with confluent mucositis per patient treated was significantly longer after CHART than after conventional fractionation. Additionally, confluent mucositis developed earlier after the start of treatment (2.9 vs. 4.9 weeks) but also started to improve sooner (5.4 vs. 7.5 weeks after the start of treatment) after CHART than after conventional radiotherapy. The relative risk of severe mucositis was 1.7 (95% CI: 1.5, 1.93) in the CHART arm.

Wygoda et al (2009) evaluated severity of acute mucosal reactions caused by conventional (CF) and accelerated fractionation (AF) regimens.[73] Sixty-six consecutive patients (33 CF, 33 AF) with head and neck cancer were irradiated with 5 fractions in 5 days per week (CF) or with 7 fractions

in 7 days (AF) to a total dose of 70 Gy. Mucositis grading used a modified Dische system which combined morphological changes as well as functional impairment. The acute mucosal reaction was scored as 0 = none, 1 = slight erythema, 2 = marked erythema, 3 = spotted mucositis, 4 = confluent mucositis. Confluent mucositis (CM) was noted in 79% of patients in the CF group and 85% in the AF group. A significant difference in the incidence of CM between the CF and AF groups was noted, mainly in weeks 4–6 of irradiation. The relative risk for severe mucositis in the AF group was 1.08 (95% CI: 0.86, 1.35) when measuring difference between groups for both grade 3+4 mucositis (so included spotted mucositis), as defined in the methods section. This analysis was not completed for grade 4 mucositis only, which may have shown significantly higher relative risk in the AF group.

Combination of the two studies in meta-analysis found accelerated radiotherapy resulted in significantly increased incidence of severe mucositis compared to conventional fractionated radiotherapy (relative risk 1.63 (95% CI: 1.45, 1.83); $P < 0.0001$). There was significant heterogeneity in the meta-analysis ($P = 0.00029$).

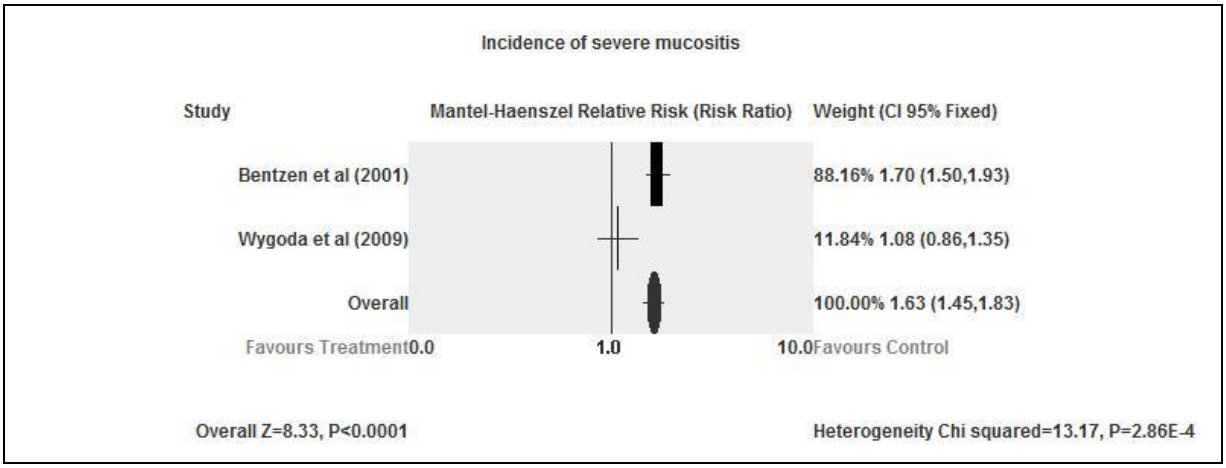

Figure 3. Incidence of severe mucositis in accelerated/hyperfractionated radiotherapy vs conventional radiotherapy for head and neck cancer.

3.2.2 Amifostine

Amifostine is a cytoprotective agent that has been investigated over a number of decades for prevention of radiation-induced toxicities.[145] Its' protective action has been attributed to its active metabolite WR-1065, which has been shown to scavenge free radicals and inactivate cytotoxic drugs.[146]

s.c. vs nothing:

Three studies, with a total of 147 participants, investigating subcutaneous (s.c.) amifostine vs nothing have been included in this review (Figure 4).[74, 89, 90]

Anne et al (2007) conducted a phase II single arm study evaluating subcutaneous (s.c.) amifostine (500 mg) once daily before radiation in conventional RT for head and neck cancer.[74] The primary outcome measured was xerostomia. The incidence of Grade 3 or worse acute mucositis was measured as a secondary outcome. Mucositis was graded according to the RTOG Acute Morbidity Scoring Criteria. Grade 3 or higher acute mucositis occurred in 18 (33%) patients. This was compared to incidence of grade 3 or worse mucositis in 60 control patients (39%) in a previous phase III trial investigating intravenous (i.v.) amifostine.[79] Relative risk of severe mucositis in the subcutaneous amifostine group was 0.85 (95% CI: 0.56, 1.30).

Braaksma et al (2005) presented an overview of costs of a chemoradiation protocol in head and neck cancer patients and an analysis of whether prevention of acute toxicity with amifostine results in a reduction to costs.[89] Fifty-four patients treated with weekly paclitaxel concomitant with radiation were randomised for treatment with subcutaneously administered amifostine (500 mg). Mucositis was measured by RTOG scoring criteria. All patients in the amifostine arm experienced grade 3 mucositis, 96% in the control arm. Relative risk of severe mucositis in the amifostine arm was therefore 1.04 (95% CI: 0.92, 1.18). The number of patients requiring a

feeding tube was identical in each group (23/27). Of note, a preliminary analysis of this study was published in 2002 by Braaksma and colleagues covering 21 patients. Being a preliminary analysis, it was not included in this review.

The oldest study investigating subcutaneous amifostine included in this review was conducted by Koukourakis et al (2000).[90] Forty patients with head and neck cancer who were undergoing radical radiotherapy were enrolled onto a randomised phase II trial to assess the feasibility, tolerance, and cytoprotective efficacy of amifostine administered subcutaneously (500 mg). A significant reduction of oropharyngeal mucositis was noted in the amifostine arm ($P < 0.04$). The delays in radiotherapy because of grade 3 mucositis were also significantly shorter in the amifostine arm compared to the group of patients treated with radiotherapy alone ($P < 0.04$). WHO grading was used to assess toxicities. No patients experienced grade 3 or 4 mucositis in the amifostine arm, compared to 30% of control patients. Relative risk of severe mucositis in the amifostine arm was therefore 0.18 (95% CI: 0.02, 1.32). Amifostine also decreased the relative risk of radiation interruptions to 0.44 (95% CI: 0.19, 1.01). In addition, this study recruited sixty patients with thoracic and 40 with pelvic tumours, although this data was not included in the current review as it did not meet inclusion criteria.

Combination of the three studies in meta-analysis found no significant protection for subcutaneous amiforstine over nothing for prevention of severe mucositis (relative risk 0.87 (95% CI: 0.69, 1.09)). There was significant heterogeneity in the meta-analysis ($P = 0.005$).

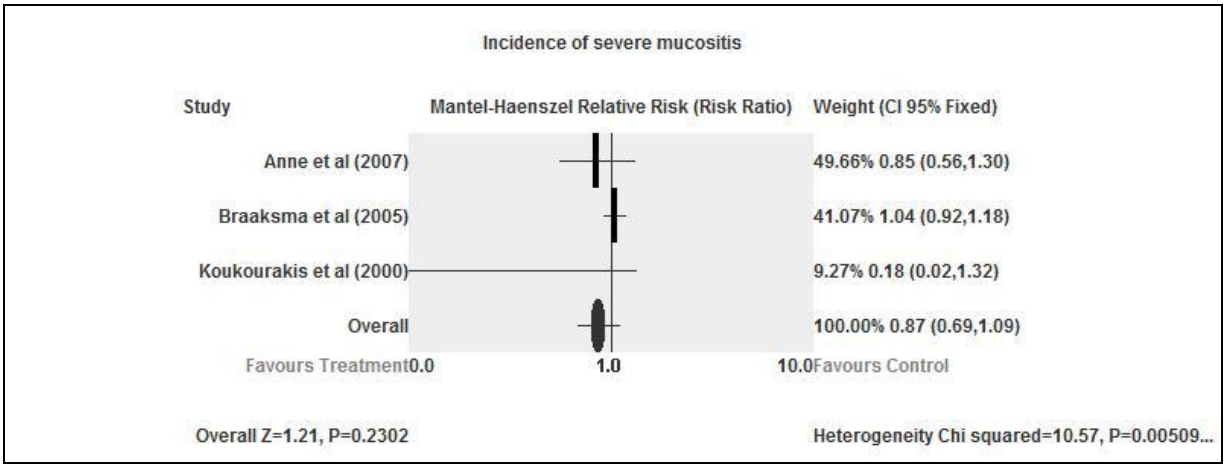

Figure 4. Incidence of severe oral mucositis with subcutaneous amifostine vs nothing in radiotherapy with or without chemotherapy for head and neck cancer.

i.v. vs nothing

A total of 8 studies, with 650 participants, evaluated intravenous (i.v) amifostine vs nothing have been included in this review (Figure 5).[79, 91-97]

Antonadou et al (2002) investigated the protective effect of amifostine in patients treated with concomitant carboplatin and conventional radiotherapy.[91] Amifostine (300 mg/m^2) was infused each day 30 minutes before radiation in 23 patients, whilst the remaining 22 patients received nothing. Mucositis was scored by the RTOG criteria weekly. By Week 6, 87% of the patients in the control group experienced Grade 4 mucositis compared with only 18.2% in the amifostine-treated group (*P*=0.0006). However, 72.7% of the amifostine patients had grade 3 mucositis at this time point, indicating that significant damage was present regardless. The relative risk of severe mucositis was 0.82 (95% CI: 0.67, 1.00) in the amifostine arm during this highly toxic regimen. All patients in the control arm experienced mucositis of some degree, whilst 2 patients in the amifostine arm did escape mucositis. The relative risk of any mucositis was therefore 0.91 (95% CI: 0.8, 1.06). Radiation treatment interruptions were decreased to 1/23 by amifostine compared to 12/22 in the control arm. As such amifostine caused a significantly reduced relative risk of 0.09 (95% CI: 0.01, 0.62).

Bennett et al (2001) investigated the clinical and economic impact of amifostine protection against the oral toxicities of carboplatin administered concurrently with standard fractions of radiotherapy.[92] Fourteen patients were randomised to receive amifostine infusion (500 mg), whilst the remaining 14 patients received nothing. Toxicity incidence differed between the groups, with patients who received amifostine having significantly less grade 3/4 mucositis compared to control patients (0% vs. 85.7%). As such, the relative risk of severe mucositis in the amifostine arm was 0.08 (95% CI: 0.01, 0.56). The scoring system used to grade mucositis was unclear, and reported as either WHO, RTOG or NCI CTC “as required”.

The study by Bourhis et al (2000) aimed to determine the protective effects of amifostine on acute mucosal injury caused by very accelerated radiotherapy for advanced inoperable head and neck cancer.[93] Twenty six patients were enrolled to receive 64 Gy in 3.5 weeks. Of these, 13 patients also received amifostine infusion (150 mg/m^2) daily before radiation therapy. Mucositis was scored according to WHO criteria. In the amifostine group, 11 out of 13 patients required a feeding tube (nasogastric tube or medical gastrostomy), because of acute mucositis, whereas in the control group a feeding tube was necessary in all cases. The relative risk of needing a feeding tube in the amifostine arm was decreased non-significantly to 0.85 (95% CI: 0.67, 1.07). The feeding tubes were in place longer in the control group (2.5 months) compared to the amifostine group (1 month). One patient in the amifostine group experienced grade 4 mucositis, compared to 8 patients in the control group. However, 10 patients in the amifostine arm had grade 3 mucositis, indicating that amifostine is unable to prevent severe mucositis completely. Since 11/13 patients in each arm experienced grade 3 or higher mucositis, the relative risk of severe mucositis when amifostine is added is 1.0 (95% CI: 0.72, 1.39). All patients experienced mucositis of some degree.

Brizel et al (2000) conducted a phase III randomised trial to test amifostine infusion (200 mg/m^2) daily during conventional radiotherapy for head and neck cancer.[79] This study enrolled 153 patients to receive intravenous amifostine, whilst the other 150 patients received no additional supportive agent. Mucositis was scored according to RTOG criteria. Mucositis was not significantly reduced in the amifostine arm. Grade 3 or 4 mucositis was experienced in 35% of amifostine-treated patients and 39% of control patients. The relative risk of severe mucositis was therefore 0.85 (95% CI: 0.63, 1.14) in the amifostine arm. Any grade mucositis was experienced in 145/153 patients in the amifstine arm compared to 149/150 patients in the control arm, indicating a relative risk of 0.94 (95% CI: 0.87, 1.01), and a non-significant protection from mucositis by amifostine.

Buntzel et al (1998) investigated the protective ability of amifostine in a phase II trial of conventional radiotherapy with concomitant carboplatin.[94] This small trial initially enrolled 14 patients to receive rapid infusion amifostine (500 mg) on the days of carboplatin administration (days 1-5, and days 21 – 25), whilst the other 14 patients received chemoradiotherapy alone. A further 11 patients were subsequently enrolled to receive amifostine based on positive results of the first 14 patients. In the control arm, 10 patients experienced grade 3/4 mucositis, compared to no patients in the amifostine arm (P<0.0001) as scored by an unclear system (potentially WHO, RTOG or NCI CTC). Relative risk of severe mucositis was therefore significantly reduced at 0.05 (95% CI: 0.01, 0.32) in the amifostine arm. Patients were treated with additional supportive agents, granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), for grade 3 leukopenia. As such, this may have altered the natural course of mucositis. Overall, only 2 patients from the amifostine group avoided any mucositis, indicating a relative risk of 0.92 (95% CI: 0.82, 1.03).

Karacentin et al (2004) conducted a randomised study of 53 patients to investigate the protective effects of amifostine in head and neck cancer treatment.[95] Thirty three patients were randomised to receive 210 mg/m^2 short infusion amifostine before each conventional radiotherapy dose. The remaining 20 patients received conventional radiotherapy alone. Grade 3 mucositis was experienced by 36.3% of patients in the amifostine arm, and 35% of patients in the control arm. As such, the relative risk of severe mucositis was 1.04 (95% CI: 0.49, 2.20) in the amifsotine arm. Indeed, 30/33 (91%) patients in the amifostine arm experienced some grade of mucositis compared to 16/20 (80%) in the control arm. The relative risk of any mucositis was therefore 1.14 (95% CI: 0.89, 1.45) in the amifostine arm.

The study by Vacha et al (2003) investigated the amifostine in patients treated with postoperative chemoradiation for head and neck cancer.[96] Conventional radiotherapy and concomitant carboplatin was administered to 25 enrolled patients. An additional 25 patients

received radiotherapy and carboplatin plus short infusion of amifostine (250 mg) immediately before the radiation dose. No mucositis incidence data was given in the study manuscript, however, the authors reported that mucosal reactions were less severe in the group treated with amifostine. Mucositis was reported as scored by the NCI CTC scale.

Veerasarn et al (2006) conducted a study on intravenous amifostine in the prevention of acute and chronic oral toxicities in patients treated by conventional radiotherapy.[97] Short infusion amifostine (200mg/m^2) was administered each day 30 minutes before radiation in 32 patients. A further 35 patients were randomised to receive radiotherapy alone. Mucositis was scored by the RTOG criteria. At the end of radiation, 36% of patients in the amifostine arm and 75% of control patients had either grade 2 or worse mucositis. The relative risk of severe mucositis in the amifostine arm was 0.46 (95% CI: 0.28, 0.78).

Combination of the studies in meta-analysis found significant protection for intravenous amifsotine compared to nothing against severe mucositis (relative risk 0.67 (95% CI: 0.56, 0.79); P <0.0001). There was significant heterogeneity in the meta-analysis (P = 0.0). There were considerable differences in the variences between study results, with 4 showing no protection, and 3 studies showing between modest and high level protection.

i.v. vs placebo

Finally, a single study was included which investigated i.v. amifostine vs placebo. Buentzel et al (2006) conducted a multicentre phase III randomised clinical trial of amifostine in prevention of oral mucositis during radiochemotherapy for head and neck cancer.[98] A relatively high dose of amifostine was administered, 300 mg/m^2, on the days carboplatin was delivered, with 200 mg/m^2 being administered on the remaining days of radiation. Mucositis was scored according to RTOG criteria. From 18 study centres, 132 patients were enrolled and randomised to either amifostine (67) or placebo (65). Grade 3 or higher acute mucositis occurred in 39% of patients

who received amifostine and 22% of patients who received placebo (P = 0.055). The relative risk of severe mucositis in the amifostine arm was however non-significantly increased at 1.73 (95% CI: 0.99, 3.03). Overall, 62/67 (93%) patients experienced any mucositis in the amifostine arm. In the placebo arm, 64/65 (98%) patients experienced mucositis of some degree. The relative risk of any mucositis in the amifsotine arm was 0.92 (95% CI: 0.87, 1.01).

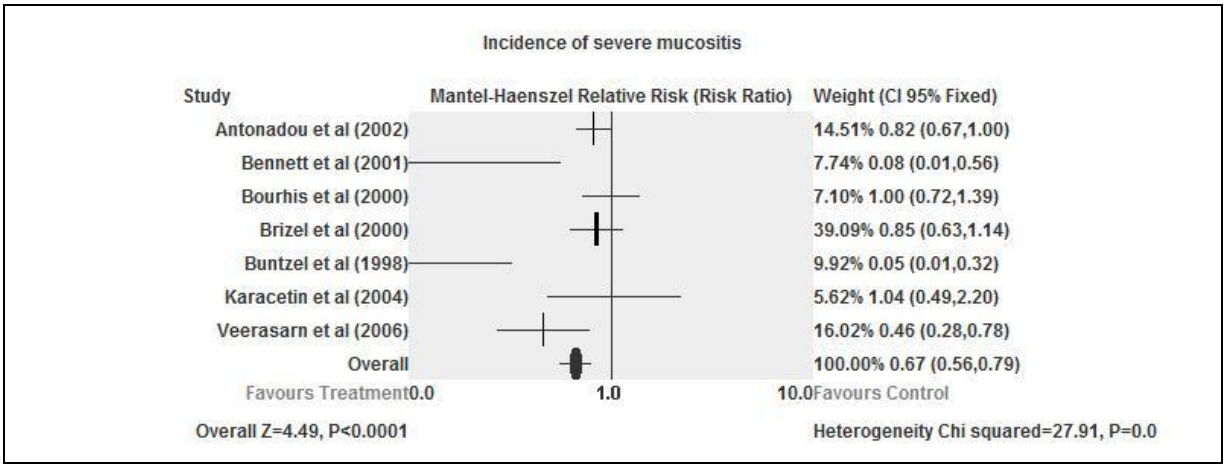

Figure 5a. Incidence of severe mucositis in patients treated with intravenous amifostine vs nothing during radiotherapy with or without chemotherapy for head and neck cancer.

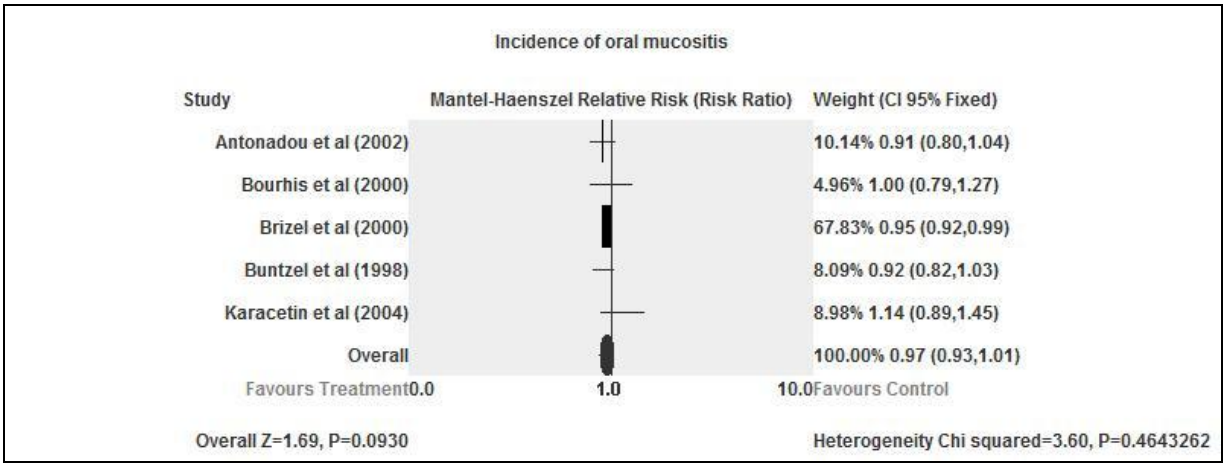

Figure 5b. Incidence of any mucositis in patients treated with intravenous amifostine vs nothing during radiotherapy with or without chemotherapy for head and neck cancer.

3.2.3 Allopurinol

Allopurinol inhibits xanthine oxidase, having antioxidant effects. It has been investigated for its potential to protect tissue during oxidative stress and in various disease states by numerous researchers.[147]

Abbasi Nazari et al (2007) investigated allopurinol mouthwash vs placebo in the prevention of oral mucositis during radiotherapy for head and neck cancer in 24 patients.[99] The mouthwashes contained Tween 80 (500 mg), Avicel (5 gm) and Xanthan (2 gm), Methyl paraben (1.8 gm), Propyl paraben (200 mg), Disodium hydrogen phosphate (2 gm), Dihydrogen sodium phosphate (3 gm) and Distilled water, with or without allopurinol powder (3 gm). All patients used the mouthwash three times per day throughout the radiation period. There was a significant difference between the two groups in proportion of patients experiencing severe mucositis in the third, fourth, fifth and sixth week of treatment. The relative risk of severe mucositis in the allopurinol arm was 0.27 (95% CI: 0.09, 0.77). Patients that experienced hypersensitivity to the mouthwash were excluded from the study, however it is unclear what proportion of enrolled patients were affected. In addition, the authors state that patients complaining of severe mucositis were excluded from the study and allowed more aggressive supportive measures. It is unclear what effect this may have had on the final results. All patients in the placebo mouthwash arm experienced mucositis of some degree during the treatment. Two patients in the allopurinol arm avoided mucositis, as such the relative risk of any mucositis was 0.86 (95% CI: 0.69, 1.06).

3.2.4 Aloe Vera

Aloe vera gel or juice is extracted from the aloe vera plant and often used in skin creams. It's cheap cost and favour with patients has meant it has been studied for prevention of radiation dermatitis[148], and more recently, oral mucositis. The mechanism of action is not well established, with one hypothesis that aloe vera may have anti-inflammatory properties through the inhibition

of cyclooxygenase.[149] Two papers with a total of 119 participants, have investigated aloe vera vs placebo in the prevention of oral mucositis during radiotherapy for head and neck cancer (Figure 6).[84, 100]

Puataweepong et al (2009) conducted a randomised clinical trial of 61 patients examining aloe vera juice during conventional radiotherapy with or without chemotheapy for head and neck cancer.[100] Patients in the aloe vera arm (31) were instructed to consume 15 ml of the juice three times a day throughout the radiation period and 8 weeks during follow up. Patients in the aloe vera group had a significantly lower incidence of severe mucositis (53%) than patients in the placebo (87%) (P = 0.004) as scored by RTOG criteria. The relative risk of severe mucositis in the aloe vera arm was 0.61 (95% CI: 0.43, 0.88). However, significantly more patients in the placebo arm had undergone previous surgery than the aloe vera arm (38% vs 13%), indicating that the groups were not well matched at baseline. Out of the entire study, only one patient in the aloe vera arm escaped having mucositis. As such, the relative risk of any mucositis in the aloe vera arm was 0.97 (95% CI: 0.90, 1.03).Aloe vera did not significantly reduce the need for radiation interruption, with 1/30 in the aloe vera group and 4/31 patients in the placebo group having a break (relative risk 0.26 (95% CI: 0.03, 2.18)).

Su et al (2004) also conducted a randomised clinical trial of aloe vera juice in patients treated with radiotherapy with or without chemotherapy.[84] In this study, patients randomised to the aloe vera arm (28) were instructed to swish and swallow 20 ml of aloe vera juice three times a day for the duration of radiotherapy. Placebo patients (30) administered a solution with the aloe vera juice replaced by water in an identical manner. Mucositis was scored by RTOG criteria. There was no statistically significant difference between the two groups for mucositis severity. The relative risk of severe mucositis in the aloe vera group was 0.88 (95% CI: 0.72, 1.07).

Combination of the two studies in meta-analysis found significant benefit for use of aloe vera compared to placebo in prevention of severe mucositis (relative risk 0.75 (95% CI: 0.62, 0.91); *P* = 0.0034).

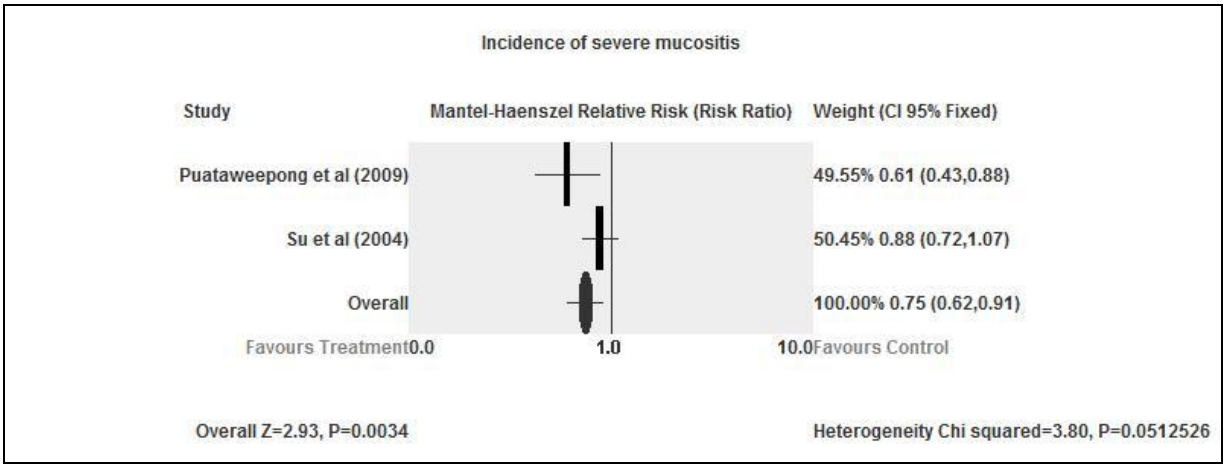

Figure 6. Incidence of severe mucositis in patients administered aloe vera vs placebo during radiotherapy with or without chemotherapy for head and neck cancer.

3.2.5 BCoG lozenge

El-Sayed et al (2002) investigated BCoG lozenges vs placebo.[101] BCoG lozenges contain a combination of bacitracin, clotrimazole, and gentamicin which suppresses gram positive cocci, gram-negative bacilli and yeast, factors thought to modulate the severity of oral mucositis.[150] One hundred thirty-seven patients were randomised to treatment with either antimicrobial lozenges (69) or placebo lozenges (68), which they consumed one per day for the duration of radiotherapy. There were no statistically significant differences between the arms in the extent of severe mucositis, time to development of severe mucositis (measured using the OMAS), or in radiotherapy delays. The relative risk of severe mucositis in the BCoG arm was 0.9 (95% CI: 0.63, 1.28), any mucositis 0.86 (95% CI: 0.33, 2.25), radiation interruption 1.23 (95% CI: 0.70, 2.17), and weighted mean difference in severity of mucositis -0.02 (95% CI: -0.12, 0.08).

3.2.6 Benzydamine

Benzydamine hydrochloride is a non-steroidal drug that has shown topical anti-inflammatory, analgesic, anesthetic and antimicrobial activities .[151] Benzydamine is currently recommended for the prevention of oral mucositis in patients receiving moderate dose radiotherapy according to the MASCC/ISOO clinical practice guidelines.[56, 57]

Benzydamine vs placebo has been investigated in two studies with a total of 226 participants.[81, 103] Epstein et al (2001) conducted a multi-institutional randomised clinical trial of benzydamine mouthwash vs placebo mouthwash in patients treated with radiotherapy (both conventional and accelerated) for head and neck cancer.[81] All patients (145) rinsed at least 4 times daily for the duration of radiotherapy, continuing for two weeks after completion. Benzydamine significantly reduced the incidence of ulcerative mucositis in patients treated with conventional radiotherapy up to 50 Gy (reported as a 26.3% reduction in mean mucositis AUC compared with placebo) (P = 0.009). However it was not effective in patients treated by accelerated radiotherapy which

caused more significant ulceration. Secondary analyses also failed to show a significant improvement overall with benzydamine. The relative risk of requiring a feeding tube placed was 0.68 (95% CI: 0.33, 1.41), and a similar non-significant reduction in radiation interruptions was noted (relative risk 0.73 (95% CI: 0.27, 1.95)). A second study by Kazemian et al (2009) investigated efficacy of benzydamine mouthwash in patients treated by conventional radiotherapy.[103] All patients (81) rinsed with 15 mL of mouthwash for 2 min, 4 times a day from the first day of RT to the end of the treatment. There was a statistically significant difference in grade 3 mucositis in the two groups, which was 43.6% (n = 17) in the benzydamine group and 78.6% (n = 33) in the placebo group (P = 0.001). As such, the relative risk of severe mucositis was 0.55 (95% CI: 0.38, 0.82).

Benzydamine vs chlorhexidine in an oral care protocol has been studied by Cheng et al (2006) in fourteen patients.[102] Patients had either chlorhexidine (n = 7) or benzydamine (n = 7) added to a standardised oral care protocol. The protocol included tooth brushing using the Bass technique and mouth rinsing with the assigned oral rinse in the early morning and at bedtime; normal saline rinsing within 30 minutes of meals; and normal saline rinsing every 4 hours during daytime from the first day to 2 weeks after the completion of radiotherapy. There was no significant difference between groups, with 43% and 29% of patients developing grade 3 mucositis, respectively. No patients experienced grade 4 mucositis, although all patients experienced some degree of mucositis as graded by the WHO scale. The relative risk of severe mucositis was 0.67 (95% CI: 0.16, 2.84) in the chlorhexidine group showing that benzydamine was not effective in this setting of radiotherapy for head and neck cancer.

3.2.7 Chlorhexidine

Chlorhexidine is a potent antimicrobial, which is effective at low concentrations and has the ability to reduce plaque.[152] The use of this agent for reducing oral mucositis in cancer patients

has been studied extensively over the past few decades. More recently, chlorhexidine vs water was investigated by Madan et al (2008) as part of a larger study of three different alcohol-free mouthwashes for prevention of oral mucositis.[104] Patients rinsed with either chlorhexidine or water twice a day for the 6 weeks of conventional radiation. The WHO scale was used to assess severity of oral mucositis weekly. Patients treated with 0.12% chlorhexidine (19) experienced a mean mucositis severity of 2.4 compared to 2.9 in patients treated with water (20) at week 6 of radiotherapy, which was reported as not statistically significant. However, the weighted mean difference was -0.48 (95% CI: -0.82, -0.14) between the chlorhexidine group and water group, indicating a real difference did exist between groups.

3.2.8 Chemotherapy

Chemotherapy is often added to radiotherapy to act as a radiosensitiser in head and neck cancer, leading to improved survival at the expense of increased toxicity.[153] Cisplatin is the predominate chemotherapy agent used, however it is associated with a high rate of toxicity. Sarkar et al (2008) investigated cisplatin vs vinorelbine for efficacy and toxicity in 72 patients treated with conventional radiotherapy.[105] Using the RTOG scale to assess mucositis weekly, they found that vinorelbine-treated patients experienced significantly less nausea and vomiting, but there was no impact on oral mucositis. All patients experienced some degree of mucositis. Severe mucositis occurred in 10/40 patients in the cisplatin arm, whilst 4/34 experienced severe mucositis in the vinorelbine arm. The relative risk was 2.12 (95% CI: 0.73, 1.20) in the cisplatin arm.

3.2.9 Dead Sea products

The Dead Sea product, Lenom®, has been investigated for protection against radiation-induced mucosal toxicity. Matceyevsky et al (2007) recruited 24 consecutive patients with head and neck cancer to receive Lenom® mouth wash during conventional radiotherapy.[106] The active ingredients in Lenom® include Dead Sea salt, chamomile extract, thyme oil, lemon peel oil, clary

sage oil and peppermint oil. Comparisons were made with age, tumour and sex matched control patients (30). The control patients received baking soda mixed with water, or salty water for mucositis, with all conducting mouth rinses three times a day, 1 week before, during, and up to 2 weeks after the completion of radiotherapy. There were no significant differences between the two groups in incidence of severe mucositis (relative risk 0.31 (95% CI: 0.04, 2.62)) or any mucositis 0.77 (95% CI: 0.50, 1.20)). However, patients in the Lenom® arm had significantly fewer treatment interruptions (P = 0.034), with a relative risk of 0.31 (95% CI: 0.10, 0.98).

3.2.10 Epidermal growth factor

Wu et al (2009) conducted a multi-institutional, raondomised, double-blind, placebo controlled trial of epidermal growth factor (EGF) spray in 51 patients receiving primary RT, primary chemoradiotherapy, or postoperative RT for head and neck cancer.[107] EGF is an important growth factor which has been shown to maintain tissue homeostasis by regulating epithelial cell proliferation, growth, and migration, and inducing angiogenesis, which provides nutritional support for tissues particularly important for wound healing.[154] This study investigated 3 different doses of EGF (10, 50, 100 μg/ml) delivered as a twice daily oral topical spray compared to placebo spray. Oral mucositis was assessed using RTOG scale weekly. Response rates to EGF were defined as the ratio of patients who did not develop oral mucositis (ie, grade <2 by weeks 4 and 5 of RT, excluding patients whose grade 2 mucositis persisted at week 4 or 5). The response rate was significantly higher in the 50 μg/ml EGF arm compared to placebo (64% vs 37%). Grade 3 or worse mucositis was experienced in 30.8% and 33.3% of the placebo group in the fourth and fifth weeks, respectively, but was experienced by less than 20% of patients in the study groups (although not statisricallt significant). The relative risk was 0.62 (95% CI: 0.24, 1.61).

3.2.11 Flurbiprofen

Flurbiprofen is a member of the NSAID family, a class of agent which has been often studied as a mucositis intervention agent.[58] Stokman et al (2005) compared flurbiprofen tooth patch vs nothing on the development, severity and duration of oral mucositis in patients treated with curative head and neck radiation.[77] Using both the OMAS and WHO scale to assess mucositis three times weekly, they found that a significant difference could be seen between the severity of mucositis in patients administered the tooth patch (12) compared to historical controls (10) at 2 weeks of radiation, but at no other time points. The weighted mean difference in mucositis severity at the end of radiation was -0.20 (95% CI: -1.61, 0.76). Pain severity was also similar between groups at most time points, except at week 2, where pain was reported as significantly worse in the flurbiprofen group (P = 0.03). The weighted mean difference for the entire duration was 2.40 (95% CI: -0.41, 5.21).

3.2.12 Fluconazole

Fluconazole is an antifungal agent commonly used to manage candidiasis in cancer patients.[155] Nicolatou-Galiatous et al (2006) studied the effect of prophylactic vs therapeutic fluconazole on severity of mucositis in patients treated with radiotherapy with or without concomitant chemotherapy.[108] Patients in the prophylactic arm received fluconazole daily from the initiation of radiotherapy, compared to the therapeutic arm which received fluconazole for one week on the development of candidiasis. The incidence of ulcerative mucositis (RTOG grades 2 – 4) was not significantly different between the two groups. The relative risk was 0.89 (95% CI: 0.67, 1.18) in the prophylactic group. However, prophylactic fluconazole did have an effect on radiation interruptions. None out of 34 patients in the prophylactic arm required a treatment break due to severe mucositis, compared to 5 of 29 patients in the therapeutic arm, the relative risk being non-significant at 0.17 (95% CI: 0.02, 1.38).

3.2.13 Glutamine

L-alanyl-L-glutamine, a non-essential amino acid used as a major energy source for gastrointestinal epithelium[156], has been investigated in two studies with a total of 46 participants.[110, 111]

Cerchetti et al (2006) compared intravenous glutamine to placebo in the ability to prevent oral mucositis in head and neck patients treated with chemoradiotherapy.[110] They used both the WHO and OMS scales to assess mucositis, and found excellent correlation between the two tools. Glutamine resulted in a complete avoidance of very severe mucositis (grade 4 WHO) (0/15 patients) compared to 5/15 patients experiencing very severe mucositis in the placebo arm. Lower grades of mucositis were not reported. The relative risk for severe mucositis was non-significant at 0.21 (95% CI: 0.03, 1.61). In comparison, Huang et al (2000) investigated a glutamine rinse vs saline rinsing for the prevention of radiotherapy-induced oral mucositis.[111] Seventeen patients (8 in the glutamine arm and 9 in the saline arm) were instructed to rinse for 3 mins before meals and bedtime daily throughout radiotherapy. The placebo arm was reported as experienced significantly more severe mucositis than the glutamine arm (P = 0.006), 5/9 compared to 0/8. Although, the relative risk was non-significantly reduced to 0.22 (95% CI: 0.03, 1.54) with glutamine. All patients experienced some degree of mucositis.

3.2.14 Glycerin payayor

Putwatana et al (2009) investigated glycerine payayor, a Thai herbal therapy, for prevention of oral mucositis in patients treated with radiotherapy with or without chemotherapy.[125] Patients were randomly assigned to receive payayor drops (30) or benzydamine rinse (30). Oral mucositis was assessed weekly using the WHO scoring system. The severity of mucositis and pain was reported as significantly worse in the benzydamine group. The weighted mean difference was -0.88 (95% CI: -1.19, -0.57) and -0.30 (95% CI: -0.43, -0.17) respectively. No

patients in the payayor group required a treatment interruption due to mouth soreness, compared to 10 in the benzydamine group. The relative risk wassignificant at 0.14 (95% CI: 0.05, 0.41).

3.2.15 Granulocyte colony stimulating factor

Granulocyte colony stimulating factor (G-CSF) is currently used to reduce the incidence of febrile neutropenic episodes in patients treated with chemotherapy, by stimulating hematopoietic precursor cells to proliferate and differentiate into mature neutrophils.[157] G-CSF has been investigated for prevention of oral mucositis in radiotherapy patients in three studies with a total of 80 participants (Figure 7).[83, 85, 109]

Mascarin et al (1999) compared G-CSF to nothing for the prevention of mucositis in head and neck cancer patients treated with hyperfractionated radiotherapy.[109] Subcutaneous G-CSF was administered daily throughout radiotherapy and mucositis was assessed every two days using the WHO scale. This non-randomised study found that severe mucositis (determined to be grade 2 or worse mucositis for at least 3 weeks during treatment) occurred in 5/13 patients treated with G-CSF, compared to 10/13 in the controls (relative risk 0.5 (95% CI: 0.24, 1.06)). The severity of mucositis was not different between the two groups, with the weighted mean difference -0.05 (95% CI: -0.32, 0.22). The number of radiation interruptions was 3 in the G-CSF group and 9 in the control group, which was statistically significant (P <0.05), at a relative risk of 0.33 (95% CI: 0.12, 0.96).

A further two studies compared subcutaneous G-CSF and placebo. Schneider et al (1998) investigated daily G-CSF vs placebo injections in patients treated for head and neck cancer with radiotherapy.[83] Fourteen patients were entered into the study and mucositis was assessed weekly using WHO scale. Of the 8 patients treated with G-CSF, only one experienced severe mucositis, compared to 3/6 in the placebo group (relative risk 0.25 (95% CI: 0.03, 1.85)). The

worst mean mucositis score was reported as significantly higher in the placebo group at 7 weeks compared to G-CSF (P = 0.035) although no data values were presented. This study was reported to be an interim analysis. A final study analysis could not be found and may not have been completed. Su et al (2006) used a mucositis assessment scale ranging from 0 – 3 (which was similar to RTOG without grade 4) to determine the effectiveness of G-CSF compared to placebo in patients undergoing conventional radiotherapy for head and neck cancer.[85] This study was halted early due to slow accrual, with only 19 patients recruited to the G-CSF arm, and 22 recruited to the placebo arm over 4 years. The incidence of grade 3 mucositis was non-significantly lower in the G-CSF arm (4/19) compared to the placebo arm (11/21) (relative risk 0.4 (95% CI: 0.15, 1.05)). A similar proportion of patients experienced any grade mucositis between the two groups (relative risk 1.04 (95% CI: 0.83, 1.32), and the duration of mucositis was reported as significantly less in the G-CSF arm (P = 0.005).

Combination of the two studies in meta-analysis found significant benefit for G-CSF compared to placebo in prevention of severe mucositis (relative risk 0.36 (95% CI: 0.15, 0.86) P = 0.02).

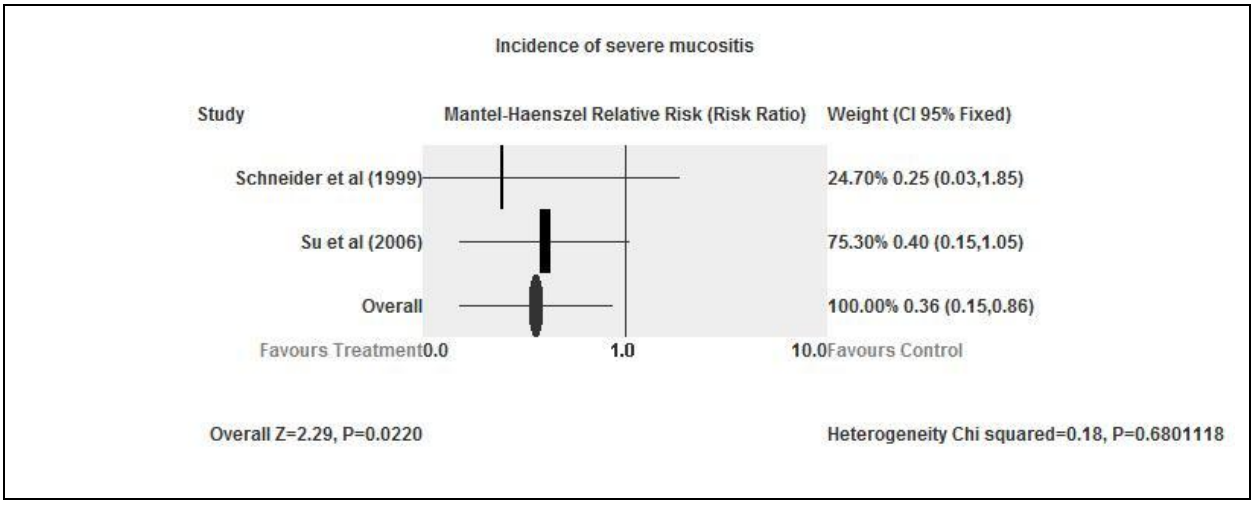

Figure 7. Incidence of severe mucositis in patients treated with subcutaneous G-CSF vs placebo during radiotherapy for head and neck cancer.

3.2.16 Granulocyte macrophage colony stimulating factor

Granulocyte macrophage colony stimulating factor (GM-CSF) enhances colony formation of granulocytes, macrophages, and eosinophils and also regulates several functions of mature leukocytes, macrophages, and dendritic cells in the dermis and submucosa.[158] It has been administered in both systemic and topical formulations to manage oral mucositis with varying success.

The first study investigated GM-CSF mouthwash vs hydrocortisone-containing mouthwash in patients treated with chemoradiotherapy.[112] Patients began the swish and swallow of GM-CSF once erythema was observed (classified as grade 1 WHO scale). Patients in the control group were treated with mouthwash containing pantocain, hydrocortisone acid, cional kreussler and bepanthen. No significant differences between the two groups in respect to grading of mucositis were observed. A total of 4/17 patients in the GM-CSF arm experienced grade 3 mucositis, compared to 7/18 in the control arm (relative risk 0.61 (95% CI: 0.22, 1.70)). Next, Saarilaliti et al (2002) investigated GM-CSF mouthwash vs sucralfate mouthwash for prevention of severe mucositis in patients undergoing post-operative radiotherapy.[113] Mouthwashes were started after a cumulative radiation dose of 10 Gy had been reached and were taken in a swish and swallow manner. Oral mucositis was assessed weekly using the RTOG scale. Although incidence data was not presented, it was reported that the mucositis scores tended to be less severe in the GM-CSF-group, most noticeable at week 6. Three patients in the sucralfate group needed hospitalization for mucositis during RT compared with none in the GM-CSF group. Additionally, 0/21 patients required a feeding tube placed in GM-CSF group compared to 2/19 in the sucralfate group (relative risk 0.45 (95% CI: 0.04, 4.60)).

Subcutaneous GM-CSF vs nothing has been investigated by McAleese et al (2006) in patients treated by accelerated radiotherapy for early laryngeal cancer.[114] GM-CSF was administered

once daily for 14 days after the second week of radiotherapy. Mucositis was assessed weekly using the RTOG scale. This study was terminated early after recruiting 29 patients due to high refusal rate. Very little severe mucositis was observed in this study, with only one patient in the control arm experiencing grade 3 mucositis (relative risk 0.93 (95% CI: 0.06, 13.54)). Furthermore, only one patient required a feeding tube in the control group (relative risk 0.93 (95% CI: 0.06, 13.54)). One patient in each group avoided mucositis all together (relative risk 1.01 (95% CI: 0.82, 1.23). Makkonen et al (2000) investigated adding subcutaneous GM-CSF to an oral care protocol containing sucralfate mouthwashes.[115] Patients received GM-CSF + sucralfate or sucralfate alone for the prevention of oral mucositis during conventional or hyperfractionated radiotherapy. Mucositis was scored on a scale from Grade 0 to 2 as follows: patients assigned to Grade 0 had no mucositis. Patients with Grade 1 had moderate mucositis as shown by erythema with edema but without ulcerations, and mucositis did not interfere with food intake or the use of dental prosthesis. Patients with Grade 2 mucositis had severe mucositis, in which the oral mucosa had one or more ulcerations or was bleeding, or mucositis interfered with food intake or the use of dental prosthesis. All patients experienced some degree of mucosal change due to radiotherapy. After three weeks of therapy 12/20 patients in each group experienced severe mucositis (relative risk 1.0 (95% CI: 0.66, 1.66)).

3.2.17 Honey

Three studies, with a total of 120 participants, have investigated honey for prevention of oral mucositis in head and neck cancer patients (Figure 8).[116-118]

Biswal et al (2003) investigated topical application of honey vs nothing in patients treated with conventional radiotherapy.[116] Grade 3 to 4 mucositis (assessed by RTOG) was significantly reduced in patients who smeared honey on the insides of their mouth 3 times daily (20%) compared to controls (75%) (relative risk 0.27 (95% CI: 0.11, 0.66)). Honey also reduced the

incidence of any grade mucositis compared to nothing (16/20 vs 19/20). No patients required a treatment interruption in the honey group compared to 4 in the control group (relative risk 0.25 (95% CI: 0.03, 2.05)). A similar study conducted by Rashad et al (2009) compared topical honey vs nothing in patients treated with chemoradiotherapy.[118] Honey significantly decreased the incidence of severe mucositis (15%) compared to the control group (65%) (relative risk 0.25 (95% CI: 0.08, 0.75)). All patients in the control group experienced some degree of mucositis (20/20), compared to 17/20 in the honey group (relative risk 0.85 (95% CI: 0.71, 1.02). No patients in the honey group required a treatment interruption or feeding tube placed compared to 5 in the control group (relative risk 0.2 (95% CI: 0.03, 1.56)). A final study investigated honey in the same number of patients using the same protocol as the previous two studies except that patients in the control group were requested to rinse with saline before and after radiotherapy.[117] Mucositis severity was assessed using OMAS and the authors reported that it was significantly lower in the honey group than the control group. No incidence data was presented to enable a relative risk calculation.

Combination of the two studies of honey vs nothing in meta-analysis showed a significant benefit for prevention of severe mucositis (relative risk 0.26 (95% CI: 0.15, 0.86); P = 0.0002), any mucositis (relative risk 0.85 (95% CI: 0.735, 0.98); P = 0.03), and radiation treatment interruption (relative risk 0.22 (95% CI: 0.05, 0.96); P = 0.0456).

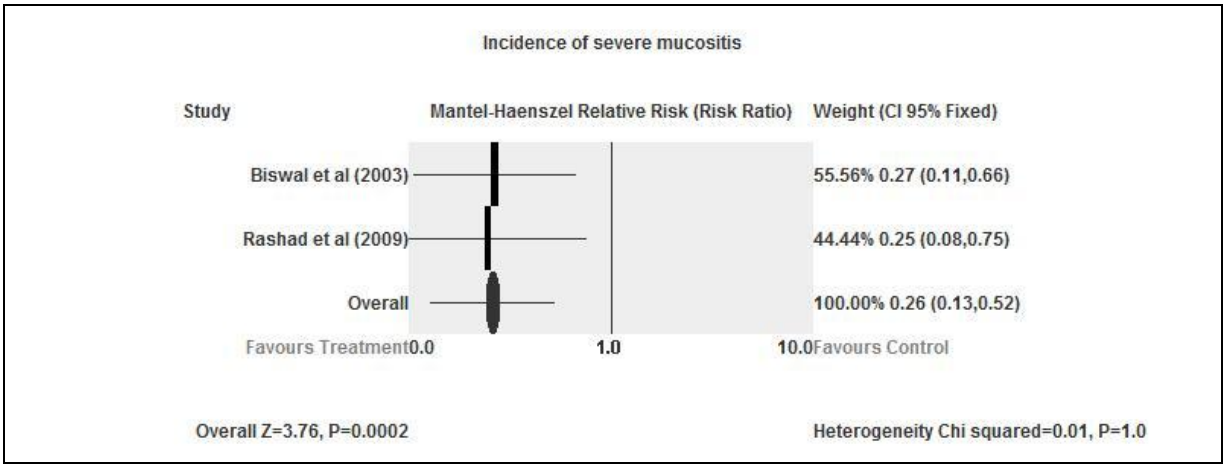

Figure 8a. Incidence of severe oral mucositis in patients treated with honey vs nothing during radiotherapy for head and neck cancer.

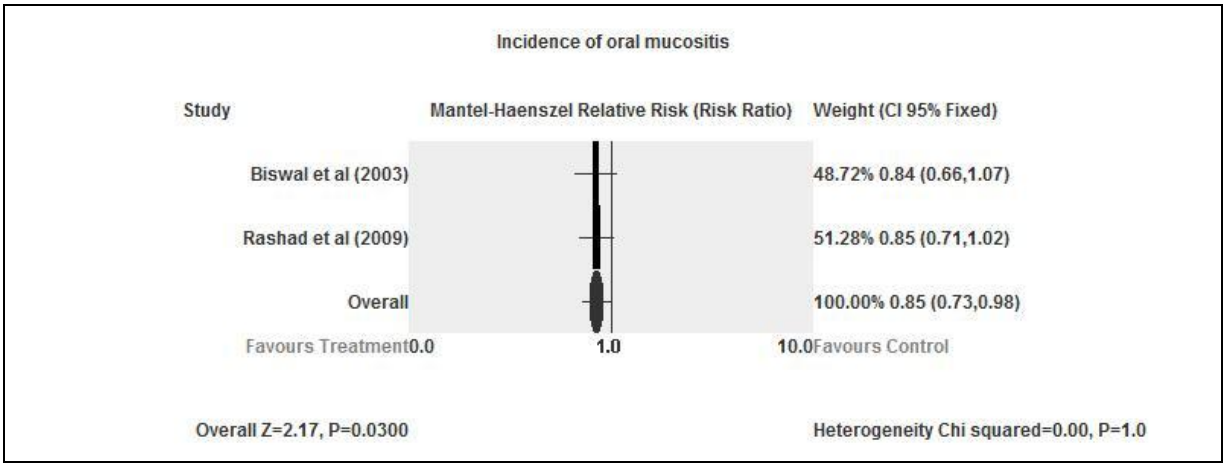

Figure 8b. Incidence of any mucositis in patients treated with honey vs nothing during radiotherapy for head and neck cancer.

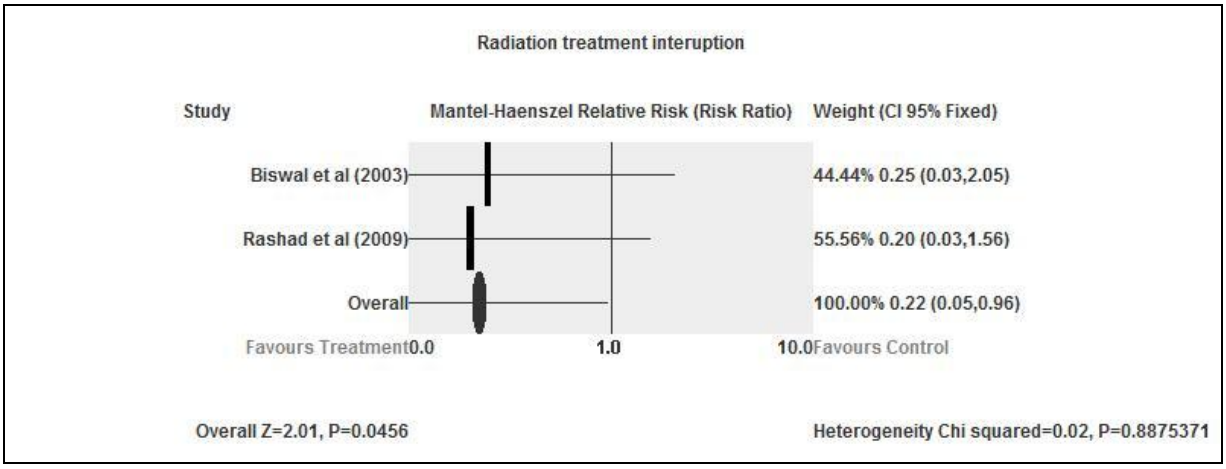

Figure 8c. Incidence of radiation treatment interruption in patients treated with honey vs nothing during radiotherapy for head and neck cancer.

3.2.18 Indigowood root extract

Indigowood root extract is a commonly used Chinese herb to remove toxic heat and to relieve convulsions.[119] You et al (2009) compared indigowood root vs saline in 20 patients treated with radiotherapy with or without chemotherapy for head and neck cancer.[119] Eleven patients swished and swallowed the indigowood root solution daily before meals, and nine patients did the same in the saline group. Mucositis was assessed by the NCI CTC scale. All patients experienced some degree of mucositis during therapy. Seven patients in each group required a treatment break (relative risk 0.95 (95% CI: 0.50, 1.82)). Severe mucositis was experienced by one patient in the indigowood root group compared to 6 in the control group (relative risk 0.14 (95% CI: 0.02, 0.93)).

3.2.19 Iseganan hydrochloride

Trotti et al (2004) conducted a large multinational clinical trial investigating iseganan hydrochloride for protection against oral mucositis in 424 head and neck cancer patients.[86] Iseganan has been shown to have rapid microbicidal activity in saliva, and is microbicidal against a broad spectrum of endogenous oral flora including Gram-positive and Gram-negative bacteria and yeast.[159] Patients were randomly allocated to either swish and swallow iseganan or placebo groups. An additional standard of care group was included in the study although the results are not included in this review. Incidence and severity of mucositis was similar between the two groups. A total of 230/253 in the iseganan arm compared to 155/171 in the placebo arm experienced some degree of mucositis (relative risk 1.0 (95% CI: 0.94, 1.07)). Severe mucositis (as assessed by NCI CTC scale) was experienced in 167/253 patients in the iseganan arm compared to 101/171 in the placebo arm (relative risk 1.12 (95% CI: 0.96, 1.30).

3.2.20 Keratinocyte growth factor

Recombinant human KGF (palifermin) is currently recommended for the prevention of oral mucositis in patients receiving high dose conditioning therapy for haematopoietic stem cell tansplant.[56] Its' mechanism of action is believed to be due to the mitogenic and anti-apoptotic properties it exerts on the gastrointestinal mucosa.[160] Brizel et al (2008) investigated palifermin in head and neck cancer patients treated with chemoradiation.[78] Sixty-seven patients were randomly allocated to receive an intravenous bolus injection of palifermin 3 days before the start of each week of radiotherapy. Another 32 patients received injections of placebo. Mucositis was assessed by the NCI CTC scale weekly. Palifermin did not significantly reduce severe mucositis, which 66% of patients experienced compared to 81% in the placebo group (relative risk 0.81 (95% CI: 0.6, 1.03)). A subgroup analysis showed that patients receiving hyperfractionated radiotherapy found more protection from palifermin than standard radiotherapy patients. In addition, treatment breaks were less common, although not significantly, in the palifermin group 28% vs 45% in the placebo group (relative risk 0.65 (95% CI: 0.38, 1.12)).

3.2.21 Low level laser therapy

Two studies have investigated low level laser therapy (LLLT) using low level Helium-Neon (He-Ne) laser for prevention of oral mucositis in patients with head and neck cancer, with a total of 80 participants.[121, 122] Arun Maiya et al (2006) compared LLLT vs saline and povidone-iodine rinses for protection against oral mucositis in patients treated with conventional radiotherapy.[121] The laser was administered at wavelength 632.8 nm and output of 10 mW five times a week before each radiotherapy session. Control patients were managed with oral analgesics and local application of anaesthetics, and 0.9 per cent saline and povidine mouthwash. Mucositis severity was significantly reduced in the LLLT group (1.72 ± 0.67) compared to the control group (3.32 ± 0.69) at the end of radiotherapy (weighted mean difference 1.60 (95% CI: -1.98, -1.22)). The

severity of pain was significantly less in the LLLT group (weighted mean difference -4.08 (95% CI: -4.70, -3.46)). All patients (25/25) in the control group experienced severe mucositis (WHO grade 3 or 4) compared to no patients (0/25) in the LLLT group (relative risk 0.04 (95% CI: 0.01, 0.27)). Seventeen patients in the LLLT group avoided mucositis completely. In comparison, Bensadoun et al (1999) compared LLLT to sham laser treatment in patients treated with radiotherapy.[122] The laser was administered at 632.8 nm and 25 mW or 60 mW (depending on institution) daily before each radiotherapy session. LLLT significantly reduced the severity of oral mucositis, with the mean grade of mucositis during radiotherapy being 2.1±0.26 for the group without laser and1.7± 0.26 for the group with laser (weighted mean difference 0.4 (95% CI: 0.21, 0.59)). Severity of pain was also significantly reduced by LLLT (1.8 ± 0.3 vs 2.02 ± 0.22) (weighted mean difference -0.22 (95% CI: -0.41, -0.03)).

3.2.22 Misoprostol

Misoprostol is a synthetic prostaglandin E_1 analogue with mucosal protective properties which has been investigated in two studies for the prevention of oral mucositis in head and neck patients.[76, 123] Johnson et al (2002) studied misoprostol in definitive and post-operative radiotherapy patients.[76] Thirty patients swished and swallowed the misoprostol mouthwash each day before radiotherapy. There was no control group in this study. Misoprostol was unable to prevent reductions in quality of life and functional assessment scores. Veness et al (2006) conducted a study with 83 patients receiving radiotherapy with or without concurrent chemotherapy investigating misoprostol vs placebo.[123] The mouthwashes were taken daily before radiotherapy and mucositis was assessed by RTOG scale. There were no significant differences between groups for incidence or severity of mucositis. From 42 patients in the misoprotol arm, 18 experienced severe mucositis compared to 17/41 patients in the placebo arm (relative risk 1.03 (95% CI: 0.62, 1.71). All patients in the misoprostol arm experienced mucositis of some degree compared to 40/41 in the placebo group (relative risk 1.03 (95% CI:

0.62, 1.71)). Indeed, mean worst mucositis pain severity was slightly higher, although not significantly, in the misoprostol arm compared to the placebo arm (7.6 vs 6.9) (weighted mean difference 0.70(95% CI: -0.06, 1.46)).

3.2.23 Morning radiotherapy

Epithelial cells of the oral mucosa have a circadian rhythm[161], knowledge of which has been exploited in an attempt to reduce radiation-induced mucosal toxicity in two recent studies (Figure 9). Bjarnason et al (2009) compared toxicity in early morning vs late afternoon radiotherapy for head and neck cancer in 205 patients.[124] The primary outcome measured was the incidence of grade 3 (RTOG) or worse oral mucositis during treatment. Fifty five (52.9%) and 63 (62.4%) patients experienced severe mucositis in the early morning and late afternoon RT groups respectively (relative risk 0.85 (95% CI: 0.67, 1.07). The severity of mucositis was also non-significantly different between the two groups (weighted mean difference -0.07 (95% CI: -0.33, 0.19)). Goyal et al (2009) found similar results in their study of morning vs afternoon radiotherapy. All 177 patients experienced some degree of oral mucositis.[144] However, slightly fewer patients experienced severe (RTOG grade 3 or worse) mucositis in the morning RT arm (23/88) compared to the afternoon RT arm (34/89) (relative risk 0.68 (95% CI: 0.44, 1.06), although not statistically significant.

Combination of the two studies in meta-analysis found a significant benefit for morning radiotherapy compared to afternoon/evening radiotherapy in prevention of severe mucositis. (relative risk 0.79 (95% CI: 0.64, 0.98); $P = 0.0324$).

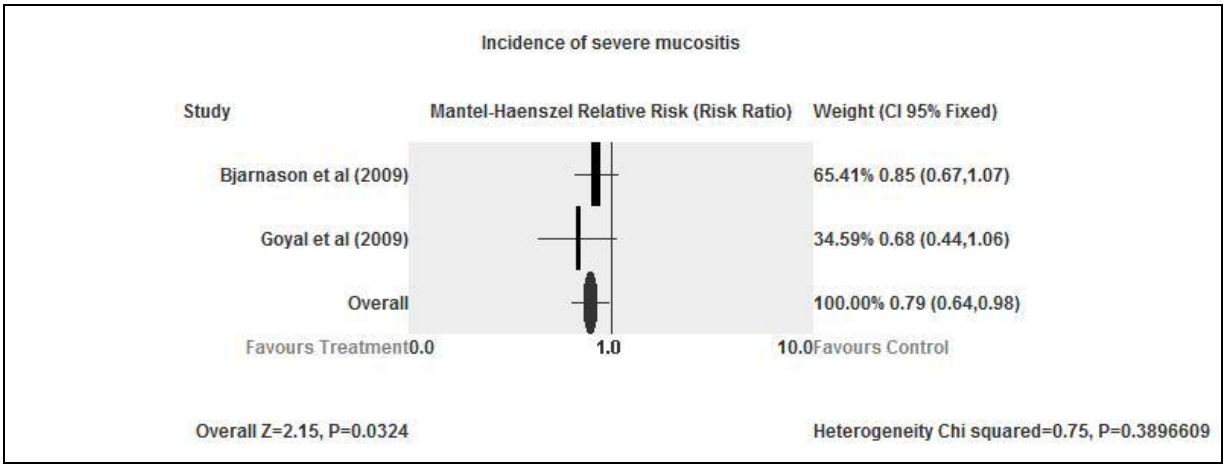

Figure 9. Incidence of severe mucositis in patients treated with radiation for head and neck cancer in the morning vs the afternoon.

3.2.24 Orgotein

Aerosol Orgotein (Ontosein®), a superoxide dismutase with anti-oxidant action, has been studied for protection against oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy. In a single arm study conducted by Escrinbano et al (2002), it was found that all patients experienced mucositis of some degree despite receiving orgotein daily throughout radiotherapy.[75] Mucositis severity peaked at week 4 with 32% (8/25) patients experiencing severe mucositis (RTOG grade 3).

3.2.25 Perio-Aid Tratamiento®

Perio-Aid Tratamiento® is a non-alcoholic mouthwash solution containing chlorhexidine (0.12%) and cetyl-pyridinium chloride (0.05%). Lanzos et al (2010) investigated this mouthwash in patients treated with conventional radiotherapy for head and neck cancer.[126] Patients were randomised to either Perio-Aid Tratamiento® (16) or placebo mouthwash (15) arms and instructed to rinse twice a day throughout radiotherapy. Oral mucositis was assessed by the RTOG scale once every two weeks from the start of radiotherapy up to 4 weeks into radiotherapy and described as change (increase, decrease, no change) from baseline. No incidence data was reported. The authors reported no significant differences between the two groups at any time point measured.

3.2.26 Pilocarpine

Pilocarpine is a parasympathomimetic drug which increases salivation, moistening the mucosa and potentially reducing irritation.[82] Two studies, with a total of 272 participants, have investigated pilocarpine vs placebo for the prevention of oral mucositis (Figure 10).[82, 127] Scarantino et al (2006) conducted a study with 245 head and neck cancer patients treated with radiotherapy.[82] Patients were randomly assigned to prophylactic pilocarpine (120) or placebo

(122), with mucositis assessed by RTOG scale. The study found no significant differences in incidence of severe (relative risk 1.08 (95% CI: 0.97, 1.20) or any mucositis (relative risk 1.06 (95% CI: 1.01, 1.12)) between the pilocarpine and placebo group. Consistently, Warde et al (2002) also found no significant difference between patients treated with pilocarpine vs placebo during radiotherapy. Fifty six percent of patients receiving pilocarpine had grade 3 or worse mucositis (RTOG) compared with 51% treated with placebo (relative risk 1.12 (95% CI: 0.81, 1.54).

Combination of the two studies in meta-analysis found no benefit for pilocarpine over placebo for prevention of severe mucositis (relative risk 1.09 (95% CI: 0.97, 1.22); $P = 0.147$).

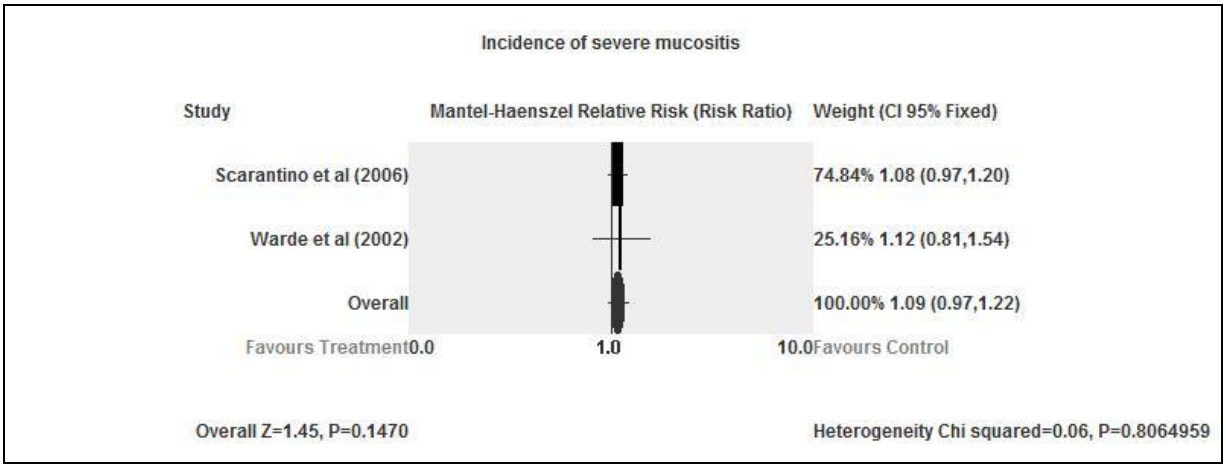

Figure 10. Incidence of severe mucositis in patients treated with pilocarpine vs placebo during radiotherapy for head and neck cancer.

3.2.27 Prednisone

Leborgne et al (1998) investigated prednisone, a corticosteroid, for the prevention of oral mucositis in patients treated with hyperfractionated radiotherapy.[128] Thirty two patients received a single daily dose of 40 mg prednisone and 34 received placebo. The mean treatment duration was significantly shorter in the prednisone arm (P = 0.013). Not surprisingly there were slightly fewer radiation treatment interruptions in the prednisone arm (7) than the placebo arm (14), although this did not reach statistical significance (relative risk 0.53 (95% CI: 0.25, 1.15)). Mucositis data could not be extracted.

3.2.28 Providone iodine

Providone iodine mouth rinse vs water has been investigated in two studies with a total of 79 participants (Figure 11).[104, 120] Adamietz et al (1998) enrolled 40 patients being treated with chemoradiation for head and neck cancer.[120] Patients were randomly assigned to receive either four daily rinses with 100 ml provodine-iodine solution (20) or 100 ml of sterile water (20). Mucositis was assessed weekly according to the WHO scale. There was a significant reduction in the mean severity of mucositis, the incidence of any and severe mucositis, and the duration of mucositis in patients treated with provodine-iodine. The incidence of severe mucositis was 4/20 in the iodine group compared to 13/20 in the water group (relative risk 0.31 (95% CI: 0.12, 0.78). All patients in the water group experienced some degree of mucositis, compared to 6 patients in the iodine group avoiding mucositis altogether (relative risk 0.7 (95% CI: 0.53, 0.93). Analysis of the raw data presented in the article found that the mean mucositis severity was 1.35 ± 1.14 in the iodine group compared to 2.7 ± 0.57 in the water group (weighted mean difference -1.35 (95% CI: -1.19, -0.79)). Madan et al (2008) enrolled patients treated with radiotherapy to received either 1% provodine-iodine or sterile water throughout therapy duration.[104] Patients

that rinsed with iodine were reported to have a significantly reduced mucositis severity compared to the water group (weighted mean difference -1.06 (95% CI: -1.45, -0.67)).

Combination of the two studies in meta-analysis found that compared to water, providone-iodine significantly reduced the severity of oral mucositis in patients treated with radiotherapy (weighted mean difference -1.16 (95% CI: -1.48, -0.83); $P < 0.0001$).

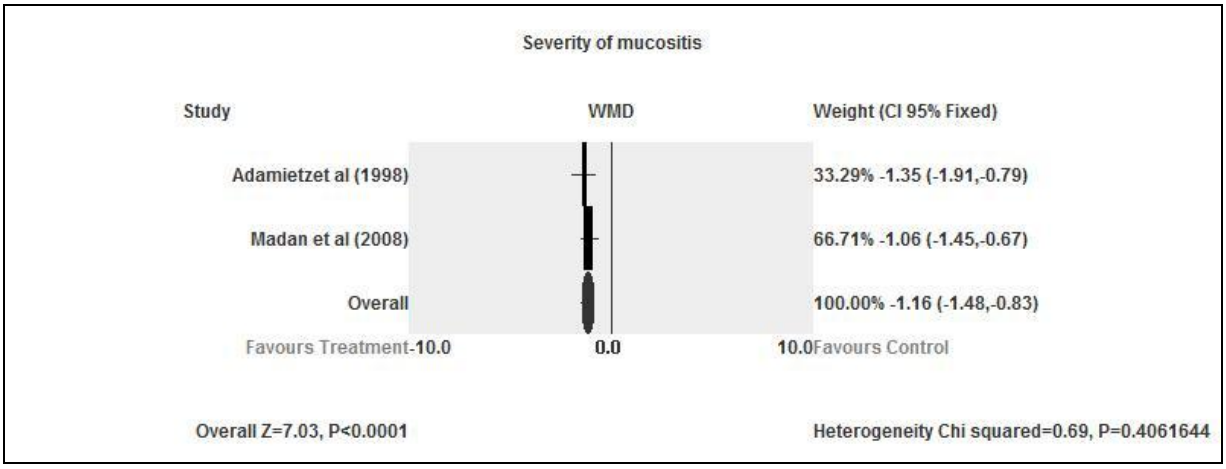

Figure 11. Severity of oral mucositis in patients treated with provodine-iodine vs water during radiotherapy with or without chemotherapy for head and neck cancer.

3.2.29 PTA

The carriage and colonisation of aerobic Gram-negative bacilli are thought to play a role in the pathogenesis of irradiation mucositis, as such selective elimination of oral flora may be effective at preventing ulcerative/infectious oral mucositis in cancer patients.[162] PTA (polymyxin E, tobramycin, and amphotericin B) administered in a lozenge was studied by Stokman et al (2003) in 65 patients with head and neck cancer treated with conventional radiotherapy.[129] Patients treated with PTA lozenge had similar severity and duration of mucositis to patients treated with the placebo lozenge as assessed by WHO scale. Placement of a feeding tube was required in 6% (2/33) and 19% (6/32) of PTA and placebo patients respectively. The relative risk of any mucositis was 0.94 (95% CI: 0.80, 1.09) in the PTA group. Wijers et al (2001) investigated PTA administered as an oral paste rather than lozenge.[130] Patients being treated with radiotherapy for head and neck cancer were randomly allocated to receive either PTA paste or placebo paste throughout duration of therapy. Mucositis grade was expressed on a 5-point scale using the van der Schueren scoring system, as follows: Grade 0, no effects on mucosa; Grade 1, slight erythema; Grade 2, pronounced erythema; Grade 3, patchy mucositis; and Grade 4, confluent mucositis.[163] No significant differences were found between groups. Severe mucositis occurred in 15/39 patients in the PTA group and 18/38 patients in the placebo group (relative risk 0.81 (95% CI: 0.48, 1.37). Any grade mucositis occurred in 82% and 89% of patients in the PTA and placebo group respectively (relative risk 0.92 (95% CI: 0.76, 1.10)).

Combination of the two studies in meta-analysis was also unable to identify any benefit with PTA compared to placebo for the prevention of severe mucositis (relative risk 0.93 (95% CI: 0.82, 1.05); $P = 0.219$) (figure 12).

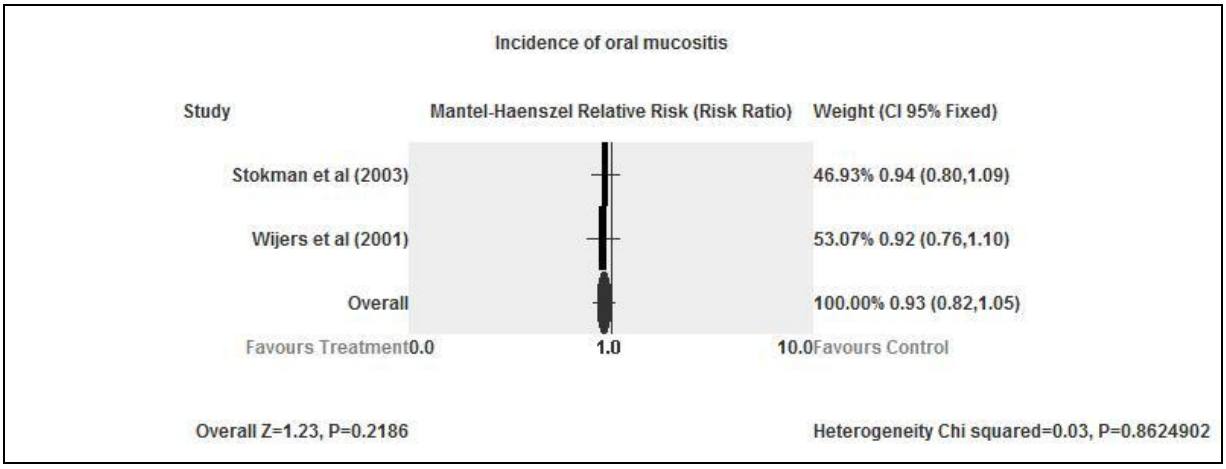

Figure 12. Incidence of any oral mucositis in patients treated with PTA paste vs placebo during radiotherapy for head and neck cancer.

3.2.30 Qingre Liyan Decoction

Qingre Liyan Decoction (QRLYD), a traditional Chinese Medicine, contains a mixture of herbs including; Flos Lonicerae, Rhizoma Belamcandae, Lasiosphaera seu Calvatia, Radix Astragali, Radix Glehniae, Radix Ophiopogonis, Radix Thrichosanthes, Radix Scrophulariae, Rhizoma Ligusticum wallichii, Herba Agrimoniae, Rhizoma Imperatae, and Radix Glycyrrhizae. Wu et al (2007) investigated QRLYD vs Dobell's solution for the prevention of oral mucositis in patients treated with conventional radiotherapy.[131] Dobell's solution is a swish and swallow mouthwash which contains sodium borate, sodium bicarbonate, phenol, and glycerol. Patients that received QRLYD had significantly less severe oral mucositis ($P < 0.05$) as assessed by RTOG scale. Five out of 30 patients in the QRLYD group experienced severe mucositis compared to 13/30 in the Dobell's group (relative risk 0.38 (95% CI: 0.16, 0.93)). QRLYD did not affect the incidence of all grade mucositis (relative risk 0.97 (95% CI: 0.90, 1.03)).

3.2.31 Salt and bicarbonate

Madan et al (2008) investigated a mouthwash containing salt and sodium bicarbonate for protection against mucositis in 38 patients treated with conventional radiotherapy.[104] From the second until the fifth week of radiotherapy, patients in the salt/soda group had significantly less severe mucositis compared to patients rinsing with sterile water. By the last week (6^{th}) of radiotherapy, the salt/soda group and water group had closer mucositis severity scores (2.5 ± 0.5 vs 2.9 ± 0.45), indicating that the protective effect was most pronounced during lower cumulative radiation (weighted mean difference -0.40 (95% CI: -0.71, -0.09)).

3.2.32 Selenium

Selenuim is a free-radiacal scavenger and therefore anti-oxidant.[164] Buntzel et al (2010) investigated selenium vs nothing in 39 patients treated with conventional radiotherapy for head and neck cancer.[132] Sodium selenite was consumed as a liquid daily throughout radiotherapy,

with mucositis assessed using RTOG. Mucositis severity was similar between groups at each week, although tended to be higher in the selenium group. The incidence of severe mucositis was not significantly higher in the selenium group (8/22) compared to control group (4/17) (relative risk 1.55 (95% CI: 0.56, 4.29). All patients experienced mucositis of some degree.

3.2.33 Sucralfate

Sucralfate, a basic aluminum salt of sucrose sulphate, is a coating agent used in peptic ulcer therapy.[165] It has been investigated for prevention of oral mucositis in head and neck cancer patients in five studies, and in an alternative formulation in one study[80, 133-137], with a total number of participants of 349 (Figure 13).

Cater et al (1999) recruited 102 patients undergoing definitive radiotherapy to swish and swallow either sucralfate (52) or placebo (50) four times daily throughout treatment.[80] No significant differences were found between groups for incidence of severe mucositis or treatment interruptions. Forty two percent and 50% of patients experienced severe mucositis (RTOG grade 3 or worse) in the sucralfate and placebo arms respectively (relative risk 0.85 (95% CI: 0.56, 1.29). The need for a feeding tube to be placed was also similar between groups, with 6/52 in the sucralfate group and 9/50 in the placebo group (relative risk 0.64 (95% CI: 0.25, 1.67)).

Cengiz et al (1999) conducted a similar study of sulcralfate vs placebo, albeit with fewer patients (sucralfate 18, placebo 10).[133] All patients experienced some degree of mucositis. No patients in the sucralfate arm experienced severe mucositis (RTOG grade 3 or worse) compared to 2 in the placebo arm (relative risk 0.28 (95% CI: 0.03, 2.70)).

Lievens et al (1999) also compared sucralfate to placebo in 83 patients receiving conventional radiotherapy for head and neck cancer.[137] Mucositis was scored using a study-specific system

described as; of 0 = none, 1 = slight enanthema, 2 = deep enanthema, 3 = spotted mucositis (<5 mm), 4 = spotted mucositis (5–10 mm), 5 = spotted mucositis (>10 mm), 6 = confluent mucositis. The study did not report incidence data, however it was stated that peak mucositis severity was not significantly different between the two groups (weighted mean difference 0.7(95% CI: -0.11, 1.51)).

A more recent study conducted by Emami et al (2008) investigated daily sucralfate vs placebo in a similar set of 52 patients.[134] In comparison to the previous studies, the investigators found a significant improvement in mucositis severity and incidence of severe mucositis (WHO grade 3) in patients administered daily sucralfate. All except two patients in the sulcrafate arm experienced some degree of mucositis (relative risk 0.92 (95% CI: 0.83, 1.03)). Fifteen out of 26 and 26/26 patients experienced severe mucositis in the sucralfate and placebo arms respectively (relative risk 0.58 (95% CI: 0.42, 0.80)). The mean peak mucositis severity was 3.05 in the sucralfate arm and 4 in the placebo arm (weighted mean difference -0.95 (95%CI: -1.36, -0.54)).

Eitz et al (2000) used the Van der Schueren scoring system to assess oral mucositis in 44 patients administered sucralfate or placebo during conventional radiotherapy.[135] Investigators found a significant reduction in the severity of mucositis in the 23 patients that received sucralfate compared to the 21 patients that received placebo (weighted mean difference =-2 (95% CI: -2.60, -1.40)). In addition, the number of patients requiring treatment interruptions was non-significantly less in the sucralfate arm (10) compared to the placebo arm (14) (relative risk 0.65 (95% CI: 0.37, 1.14)).

Evensen et al (2001) recruited patients receiving radiotherapy for head and neck cancer to rinse with Na-SOS (octasulfate) suspension or a placebo suspension throughout treatment.[136] Na-SOS differs slightly from sucralfate by being complexed with sodium rather than aluminium. Similar to the studies with sucralfate, the investigators found no significant protection against oral

mucositis afforded by Na-SOS. Using the Van der Schueren scoring system, they found all patients in the Na-SOS arm (30) experienced some degree of mucositis, compared to 28/30 in the placebo arm (relative risk 1.13 (95% CI: 0.89, 1.44)). The incidence of severe mucositis was similar in the Na-SOS arm with 26 patients experiencing grade 3 or 4 mucositis, compared to 23 patients in the placebo arm experiencing grade 3 or 4 mucositis (relative risk 1.13 (95% CI: 0.89, 1.44)).

Studies comparing sucralfate to placebo were combined in meta-analysis where similar outcomes were reported. Meta-analysis found an overall improvement in incidence of severe mucositis with sucralfate compared to placebo (relative risk 0.69 (95% CI: 0.53, 0.91); P = 0.0076), however, no difference was seen for any mucositis. Meta-analysis found a significant improvement overall for mucositis severity with sucralfate (weighted mean difference -0.99 (95% CI: -1.30, -0.68) $P < 0.0001$). Although, there was significant heterogeneity in this meta-anlaysis ($P = 0.0$).

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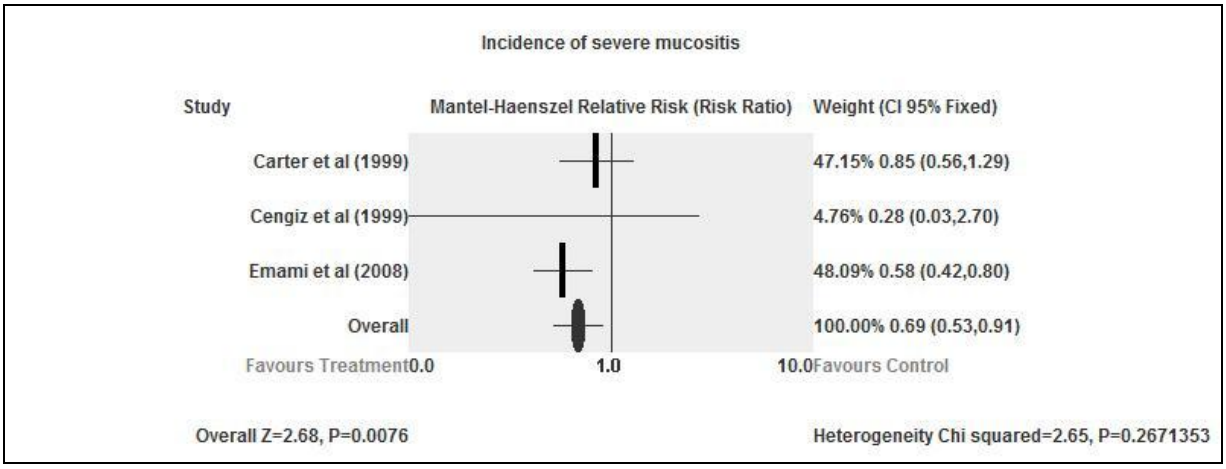

Figure 13a. Incidence of severe oral mucositis in patients treated with sucralfate vs placebo during radiotherapy for head and neck cancer.

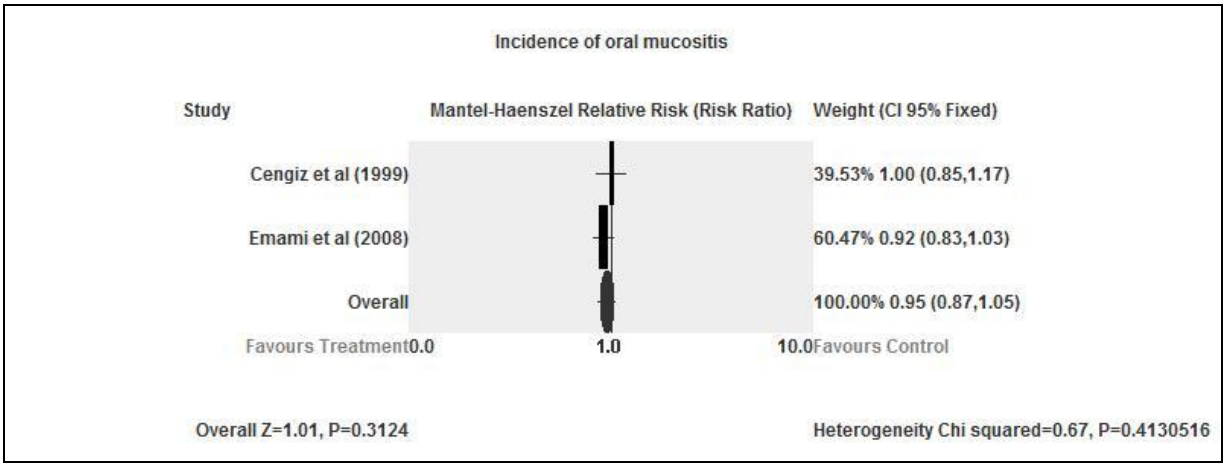

Figure 13b. Incidence of any oral mucositis in patients treated with sucralfate vs placebo during radiotherapy for head and neck cancer.

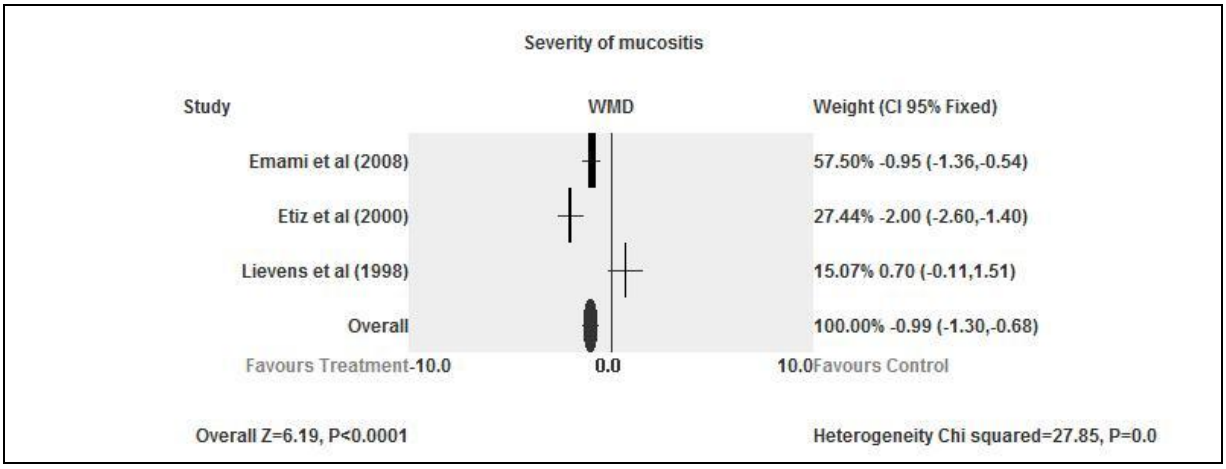

Figure 13c. Severity of oral mucositis in patients treated with sucralfate vs placebo during radiotherapy for head and neck cancer.

3.2.34 Vitamin E

Alpha-tocopherol, the main constituent of vitamin E (VE), is an antioxidant naturally present in blood.[166] Ferreira et al (2004) investigated vitamin E for the prevention of oral mucositis in 54 patients treated with conventional radiotherapy.[138] Patients were randomised to receive orally dissolved capsules containing 400 mg vitamin E (28) or 500 mg Evening Primrose Oil as placebo (26) daily for the entire duration of radiation. All patients experienced mucositis of some degree during therapy (assessed by RTOG). The amount of mucositis experienced was calculated as an incidence density (incidence per 100 patient weeks). The authors reported that symptomatic mucositis was significantly more frequent in the placebo group (33.5) than in the vitamin E group (21.6).

3.2.35 WF10

Pepattanagul et al (2007) investigated WF10 vs nothing for the prevention of oral mucositis in 13 patients receiving chemoradiotherapy.[87] WF10 (Immunokine®) is a chlorite-based drug which contains the active ingredient OXO-K993 (tetrachlorodeca-oxygen), and has been shown to be able to stimulate monocyte/macrophage phagocytosis and cellular defence systems.[167] WF10 was administered as an intravenous infusion on the days of radiation. Control patients received no intervention. All patients experienced mucositis of some degree. Only patients in the control group (2/7) experienced severe mucositis or required treatment interruptions (3/7) (relative risk 0.58 (95% CI: 0.07, 4.95) and 0.39 (95% CI: 0.05, 2.83)) respectively).

3.2.36 Wobe-Mugos E

The active ingredients of Wobe-Mugos E tablets are hydrolytic enzymes (Papain 100 mg, trypsin 40 mg, and chymotrypsin 40 mg), which have been shown to have analgesic and anti-inflammatory effects.[140] The protective effect of Wobe-Mugos E has been investigated in three studies[139-141], with a total of 220 participants (Figure 14). Kaul et al (1999) recruited patients to

take 3 tablets, 3 times per day starting 3 days before radiotherapy and extending until 1 week after completion of radiation. Control patients took nothing.[140] All but one patient in the enzyme group experienced mucositis of some degree, as assessed by the EORTC scale (relative risk 0.96 (95% CI: 0.89, 1.04)). The incidence of severe mucositis was 2/25 in the enzyme group and 6/26 in the control group (relative risk 0.33 (95% CI: 0.07, 1.50)). Gujral et al (2001) conducted a very similar study of Wobe-Mugos E vs nothing in radiotherapy patients.[139] Positive results for Wobe-Mugos enzymes were reported in this study also. The incidence of any mucositis was 51/53 in the enzyme group and 47/47 in the control group (relative risk 0.96 (95% CI: 0.91, 1.01)). Severe mucositis (EORTC grade 3) was less common in the enzyme group (3/53) than in the control group (15/47) (relative risk 0.18 (95% CI: 0.05, 0.57)). The peak severity of mucositis was decreased significantly from 2.24 ± 0.6 to 1.32 ± 0.64 in the control and enzyme groups respectively (weighted mean difference -0.92 (95% CI: -1.16, -0.68)). Dorr et al (2007) included a placebo in their study of Wobe-Mugos E for prevention of oral mucositis in 69 patients receiving conventional or hyperfractionated radiotherapy.[141] Mucositis was scored using a slightly modified RTOG classification. Patients took 4 tablets, 3 times a day throughout radiotherapy. No significant differences were found between the two groups for maximum mucositis score. The average mucositis score between week 1 and 6 of radiation were reported as significantly higher in the enzyme group. Mucositis incidence results were not given. Results were only presented in figures, preventing calculation of mean differences or relative risk.

Two studies could be combined in meta-analysis. This found that Wobe Mugos E compared to nothing has a significant benefit for prevention of severe mucositis (relative risk 0.22 (95% CI: 0.09, 0.55); $P = 0.0012$).

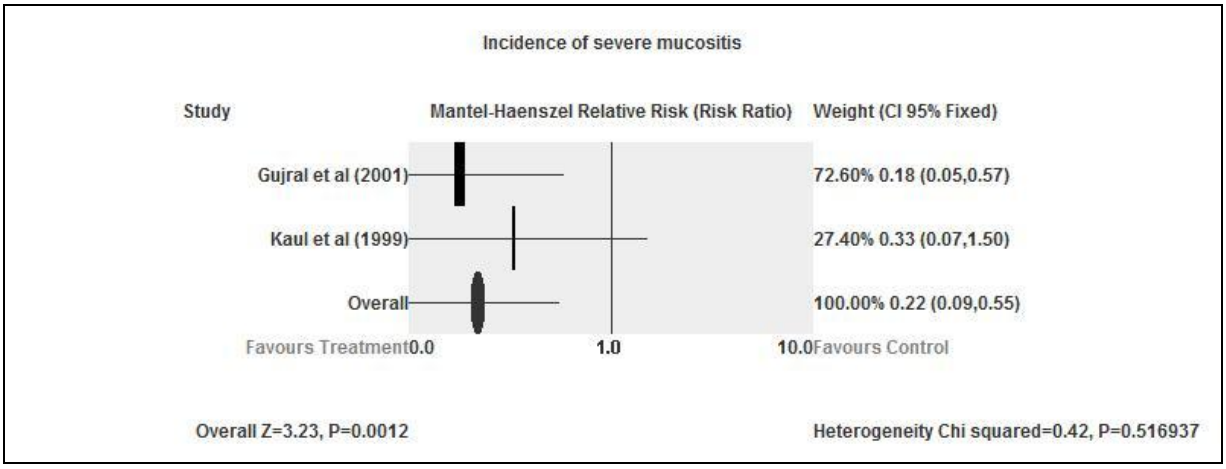

Figure 14a. Incidence of severe mucositis in patients treated with Wobe-Mugo E vs nothing during radiotherapy for head and neck cancer.

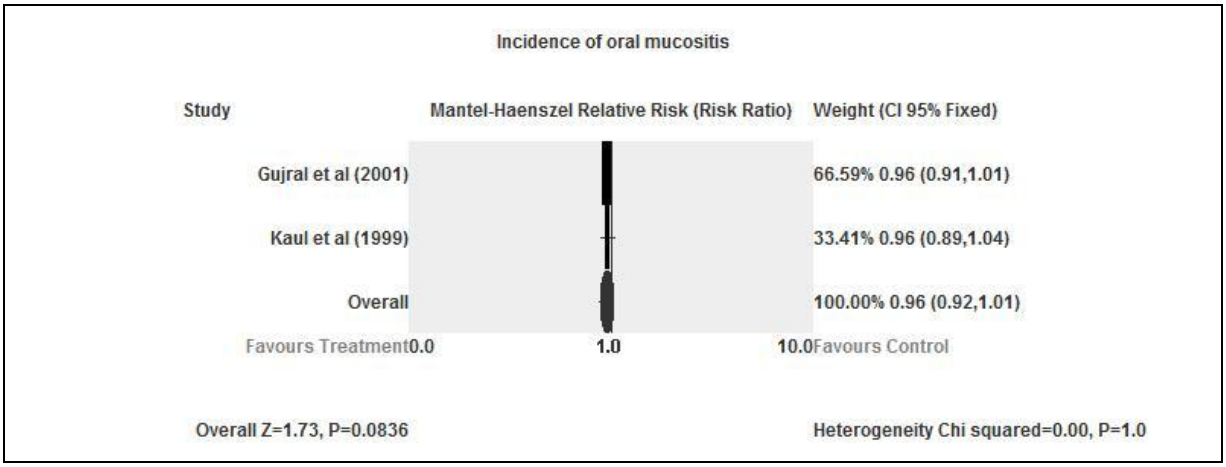

Figure 14b. Incidence of any mucositis in patients treated with Wobe-Mugo E vs nothing during radiotherapy for head and neck cancer.

3.2.37 Zinc

Two studies with a total sample size of 124, investigated zinc vs placebo for prevention of mucositis in patients receiving radiotherapy with or without chemotherapy for head and neck cancer (Figure 15).[142, 143] Ertekin et al (2004) randomly assigned patients to receive either capsules containing 50 mg zinc or placebo (empty capsules).[142] Capsules were consumed three times per day from the start of radiotherapy until 6 weeks after the completion of therapy. Mucositis of some degree developed in 13 of 15 patients in the zinc group, compared to all 12 patients in the placebo group (relative risk 0.87 (95% CI: 0.71, 1.06)). The incidence of severe mucositis (RTOG grade 3 or worse) was 8/12 in the placebo group, whereas no patients in the zinc group experienced grade 3 or 4 mucositis (relative risk 0.10 (95% CI: 0.01, 0.69)). Lin et al (2006) investigated 25 mg zinc or placebo (soybean oil) capsules taken 3 times per day from the start to the end of radiotherapy for prevention of mucositis in 97 patients.[143] Mucositis was assessed weekly using RTOG scale. Severe mucositis (RTOG grade 3) was more significantly common in the placebo group than the zinc group (P = 0.0003). Forty five percent of patients in the zinc group, and 77% of patients in the placebo group experienced grade 3 mucositis (relative risk 0.58 (95% CI: 0.41, 0.82)). Treatment interruptions were slightly more common (not significantly) in the placebo group than the zinc group (15/47 vs 12/49) (relative risk 0.77 (95% CI: 0.40, 1.46)).

The two studies were pooled for meta-analysis and found a statistically reduced risk of severe mucositis with zinc compared to placebo (relative risk 0.49 (95% CI: 0.35, 0.69); P <0.0001).

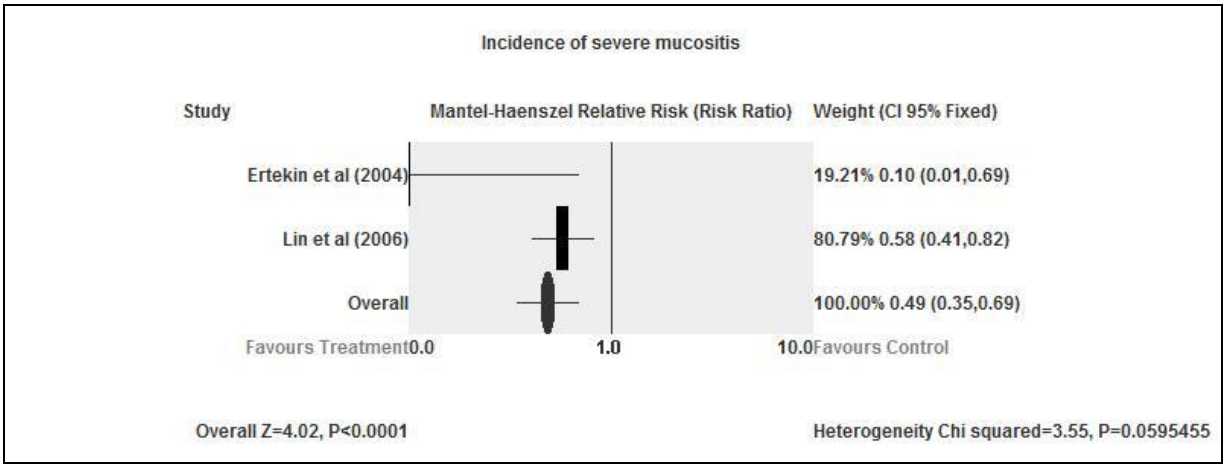

Figure 15. Incidence of severe mucositis in patients treated with zinc capsules vs placebo capsules during radiotherapy with or without chemotherapy for head and neck cancer.

Chapter 4. Discussion and Conclusions

4.1 General Discussion

The aims of this systematic review were to determine the effectiveness of oral mucositis interventions on incidence and severity of mucositis and selected complications in patients with locally advanced or metastatic head and neck squamous cell carcinoma treated with radiotherapy or chemoradiotherapy. The review identified 13 mucositis interventions with sufficient evidence to be combined in meta-analysis (accelerated radiotherapy, subcutaneous amifostine, intravenous amifostine, aloe vera, G-CSF, honey, morning radiotherapy, pilocarpine, providone-iodine, PTA, sucralfate, Wobe-Mugos E and zinc). Meta-analysis was confined to trials of the same intervention (delivered in the same way) that assessed the same outcome. In addition, comparators also needed to be sufficiently similar across studies for each intervention, so as to be satisfied that the study design was comparable. Due to the rigor in selection of studies for combination (i.e. all studies are considered to have been conducted under similar conditions with similar subjects), it was decided that a fixed effects model should be used to compare studies by meta-analysis. The lack of replication studies meant that for any intervention the maximum number of studies included in a meta-analysis ranged from 2 - 7, which in turn limited the ability to draw definitive conclusions. For many of the studies only a narrative summary was possible due to variations in the interventions, comparators, assessment scale used, or the outcomes measured. Outcomes in studies that were reported with insufficient data to complete a two by two table were described in narrative fashion if possible. Furthermore, continuous outcome data, including severity of mucositis and pain, was described in narrative manner if variance was not presented. A discussion of the interventions with sufficient evidence to conduct a meta-analysis is provided below under the specific intervention sub-heading.

ACCELERATED RADIOTHERAPY

Two studies investigated the effect of altered radiotherapy fractionation schedules on the incidence and severity of oral mucositis.[73, 88] Investigators found that accelerated and hyperfractionated radiotherapy (CHART) caused significantly more severe mucositis compared to conventional radiotherapy[88], and similarly, accelerated radiotherapy resulted in significantly increased incidence of severe mucositis.[73] Although the two studies investigated different radiotherapy schedules (accelerated and accelerated + hyperfractionated), these were combined for meta-analysis as it was considered to be investigating a common biological underpinning for risk of mucosal injury, i.e. radiotherapy delivered more frequently will increase mucosal injury. Meta-analysis found accelerated radiotherapy resulted in significantly increased severe mucositis. However, increased mucosal toxicity may be offset by improved tumour response and survival. The meta-analysis had significant heterogeneity. To test robustness of the finding, a random effects method (DerSimonian and Laird relative risk) was applied to a secondary meta-analysis and found there was no longer a significant worsening of severe mucositis with accelerated radiotherapy (relative risk 1.37 (95% CI: 0.85, 2.18). The random effects model gave relatively greater weighting (47%) to the much smaller study conducted by Wygoda et al (2009), which found no significant difference in the relative risk of grade 3 and 4 mucositis between groups. The study scoring system classified spotted mucositis as grade 3, which is generally not considered severe mucositis by accounts of the more commonly used grading systems. As such, this finding may not truly reflect the differences in severe mucositis which occurred in the accelerated radiotherapy group.

AMIFOSTINE

Amifostine was assessed in 12 studies[74, 79, 89-98], which ranged in evidence from single arm non-randomised studies to a double blind randomised controlled trial, covering multiple doses,

schedules and routes of administration (s.c. and i.v.). In general terms, amifostine was effective at significantly reducing mucositis in 5 studies[90-92, 94, 97], was ineffective in 6 studies[74, 79, 89, 93, 95, 98], and had unclear effects in one study.[96] Interestingly, in the only study where amifostine was compared to placebo, the investigators found an almost statistically significant (P = 0.055) worsening of mucositis in the amifostine-treated patients.[98] As such, the evidence for use of amifostine is conflicting, with numerous low quality studies being an inadequate basis on which to reach solid conclusions regarding its' effectiveness. This sentiment is echoed in the MASCC Clinical Practice Guidelines for prevention and treatment of mucositis which were unable to reach a concensus on recommendation for the use of amifostine for the prevention of oral mucositis due to insufficient conflicting evidence.[56] The most recent Cochrane Systematic Review of interventions for mucositis prevention concluded that there is weak unreliable evidence to support a beneficial role for amifostine.[51] In the present review, the meta-analysis of studies of subcutaneous amifostine found no significant protective effect, whereas intravenous amifostine did show significant protection against severe mucositis compared to nothing. However, this finding should be considered cautiously since the highest level of evidence study found no benefit of intravenous amifsotine, and potentially worsened mucositis.[98] That particular study was not included in the meta-analysis since the comparator was not identical to the other studies. In addition, the meta-analysis for intravenous amifostine had significant heterogeneity reflecting the large variance in study outcomes. This is due to the conflicting results found between studies. A secondary meta-analysis using random effects methodology found that the significant benefit for amifostine was retained (relative risk 0.67 (95% CI: 0.46, 0.99).

ALOE VERA

Two studies of aloe vera were combined in a meta-analysis in this review.[84, 100] Although one study found aloe vera to be beneficial, and the other showed no significant benefit of aloe vera

compared to placebo, the final meta-analysis found a significant benefit for aloe vera. This finding is consistent with Cochrane which found weak unreliable evidence that aloe vera solution was beneficial for the prevention of moderate to severe mucositis (RR 0.74 (95% CI: 0.58, 0.96); $P = 0.02$).[51]

G-CSF

Granulocyte colony stimulating factor was investigated in 3 small studies (a total of 81 patients).[83, 85, 109] Although each individual study suggested a beneficial role for G-CSF, they lacked sufficient power to identify a statistically significant effect. Combination of the two studies, which included a placebo in the study design[83, 85], into a meta-analysis found a significant benefit for G-CSF in prevention of severe mucositis. The study comparing G-CSF to nothing was excluded from the meta-analysis as the comparator was not identical. The results in the present review complement that of the 2011 Cochrane systematic review, which found weak evidence that G-CSF is effective for the prevention of severe mucositis (relative risk 0.36 (95% CI: 0.13, 0.52); $P = 0.02$).[51]

HONEY

Two studies of honey vs nothing[116, 118] were combined in a meta-analysis which showed a significant benefit for prevention of severe mucositis, any mucositis, and radiation treatment interruption. These findings are supported in the Cochrane Systematic review of interventions for the prevention of oral mucositis.[51] The authors discussed the limitations of the study design in respect to the consistency of honey preventing application of a suitable placebo. As such, it is unclear from this research whether the honey itself was protective, or rather the barrier properties preventing irritation and hence development of ulceration. A third study which reported significant beneficial effects of honey[117] could not be included in the meta-analysis as incidence data for severe mucositis could not be extracted.

MORNING RADIOTHERAPY

Two studies investigating the effect of morning radiotherapy compared to evening radiotherapy on severe mucositis were included in a meta-analysis.[124, 144] Both studies found a non-significant improvement in incidence of severe mucositis with the morning radiotherapy, however the meta-analysis found a significant overall weak benefit. These two studies included a combined total of 428 patients which was the largest number for any interventions. Despite the interesting results to date, this approach to reducing oral mucositis requires further investigation, and additional consideration of the relative difficulty in clinical implementation.

PILOCARPINE

The incidence of oral mucositis has been investigated as a secondary outcome in two clinical trials of pilocarpine.[82, 127] The best studied effect of pilocarpine is in relief of xerostomia, although since oral lubrication and maintenance of oral hygiene is considered important in the pathogenesis of mucositis, this intervention may be effective. However, both studies failed to show any significant benefit for pilocarpine in comparison to placebo for reducing severe mucositis, which was also demonstrated within the final meta-analysis. Therefore there is no evidence from these two studies that pilocarpine is more or less effective than placebo in preventing mucositis.

PROVIDONE IODINE

Two studies provided evidence for a benefit of providone-iodine in reducing severity of oral mucositis, both alone and when combined in meta-analysis.[104,120] Compared to water, providone-iodine significantly reduced the severity of oral mucositis in patients treated with radiotherapy. This agent has a distinctive colour and taste, preventing patient blinding to intervention. This increases the risk of bias significantly and consequently reduces the level of the evidence. Future

studies with an appropriate placebo are required to clarify the protective role of providone-iodine.

PTA

PTA (polymyxin E, tobramycin, and amphotericin B) anti-microbial/anti-fungal combination was investigated for prevention of oral mucositis in two studies[129, 130], with results pooled in a meta-analysis. Neither study was able to provide a significant improvement with either PTA lozenge or paste compared to placebo. The meta-analysis was also unable to identify any benefit with PTA. As such, to date there is substantial evidence to indicate that locally applied PTA provides no protection from oral mucositis in head and neck cancer patients treated with radiotherapy. In support, the MASCC mucositis guidelines recommend that antimicrobial lozenges not be used for the prevention of radiation-induced oral mucositis.[56] It is important to note that older systematic reviews drew a different conclusion. In the meta-analysis conducted by Sutherland et al (2001), a significant benefit for PTA lozenges (odds ratio 0.45 (95% CI: 0.23, 0.86)) was found following positive results in two clinical trials.[168, 169] In addition, the meta-analysis conducted by et al (2006) found an overall benefit for PTA lozenge, when the outcome "presence of ulceration" was considered (odds ratio 0.61 (95% CI: 0.39, 0.96)).[62] That meta-analysis included studies that recruited patients with a variety of tumours, and also included one study that investigated BCoG lozenge rather than PTA.[101] Since subsequent clinical trials have shown no benefit for PTA, it highlights the importance of regular updates of systematic reviews and clinical practice guidelines when considering appropriate implementation of any mucositis intervention.

SUCRALFATE

Of the five studies of sucralfate versus placebo included in this review[80, 133-135, 137], three could be aggregated in a meta-analysis for effect on severe mucositis any mucositis and severity of mucositis. The only study that showed an increase in mucositis severity with sucralfate was

conducted by Lievens et al (1998). The authors reported poor compliance in the sucralfate arm, indicating less tolerance to the intervention compared to placebo.[137] Of note, the study found a non-significant difference in peak mucositis severity at week 5, a time when maximal mucositis is often noted, between the two groups, with the sucralfate-treated patients roughly one full point below the placebo patients (mucositis scored 0 – 6). However, this was not reflected in the mean peak severity score, where sucralfate was higher. It is unclear if the results were reported incorrectly here. Regardless of this conflicting study, the meta-analysis found a significant improvement overall for mucositis severity with sucralfate. This study also contributed to the heterogeneity in the meta-analysis. An additional meta-analyses using random effects methodology, which gave the three studies equal weighting, found that the benefit for sucralfate was not significant (weighted mean difference -0.79 (95% CI: -2.05, 0.49). Meta-analysis found an overall improvement in incidence of severe mucositis with sucralfate, but no difference for any mucositis. There was no significant heterogeneity in these meta-analyses. . This finding is similar to Cochrane which stated that substantial evidence exists supporting sucralfate as an effective intervention for the prevention of severe mucositis (relative risk 0.67 (95% CI:0.48 to 0.92), $P = 0.01$).[51] In contrast, the meta-analysis conducted by Stokman et al (2006) did not find a significant benefit for sucralfate (odds ratio 0.82 (95% CI: 0.05, 1.33)), when results from 9 studies were pooled.[62] The differences in methodology between the systemiatic reviews are the cause for the variance in conclusions for sucralfate.

WOBE-MUGOS E

Results of two studies of the combination hydrolytic enzyme tablet, Wobe-Mugos E, could be pooled into a meta-analysis.[139, 140] When compared to nothing, Wobe-Mugos E showed significant benefit for prevention of severe mucositis. Although, it should be noted that only Gujral et al (2001) found a significant improvement of severe mucositis within the study.[139] What's more, a recent placebo controlled study was unable to show any protection with the

enzymes during radiotherapy.[141] Although no incidence data was presented, the average mucositis score between week 1 and 6 of radiation was stated as significantly higher in the Wobe-Mugos E group. As such, it is unclear whether use of these enzymes for prevention of oral mucositis is warranted. In support, the Cochrane review also concluded that there is insufficient evidence that the use of hydrolytic enzymes to prevent mucositis associated with radiotherapy for head and neck cancers is significantly different from placebo or no treatment.[51]

ZINC

Zinc sulphate tablets were investigated in two studies which compared zinc supplementation to placebo for prevention of oral mucositis in head and neck cancer patients treated with radiotherapy with or with combined chemotherapy.[142, 143] The studies were pooled for meta-analysis and found a statistically reduced risk of severe mucositis with zinc. For the study conducted by Lin et al (2006), the two by two table for calculation of relative risk was constructed from data presented in figures since it was not given in text. As such, caution should be exercised when interpreting the results.[143] Furthermore, the authors stated that zinc supplementation was unable to prevent weight loss during radiotherapy, indicating that there was not a functional benefit despite reduced mucositis scores. Further studies of zinc supplementation are required before making judgment on the benefit, if any, of this intervention for the prevention of oral mucositis.

OTHER INTERVENTIONS

This review was unable to aggregate other interventions into a meta-analysis because of a lack of homogeneous repetition studies. However, a small number of agents have reasonable levels of evidence surrounding their use for mucositis prevention. Of note, benzydamine hydrochloride (marketed as Difflam®) was investigated in two studies, but due to a lack of consistency in reporting of outcomes, pooling of data could not be achieved. In a randomised clinical trial

comparing benzydamine to placebo, all mucositis data was reported in regards to area under the curve and percentage area at risk, which did not allow a two by two table to be constructed.[81] This is disappointing considering the current recommendation for use of benzydamine to prevent oral mucositis in head and neck cancer patients receiving moderate dose radiotherapy by MASCC.[56] On the other hand, Cochrane have a more reserved support for this agent, stating that there is weak unreliable evidence that the use of benzydamine may reduce the development of mucositis.[51]. Two studies with chlorhexidine as an intervention were included in this review, with one comparing to water [104] and the other comparing to benzydamine.[102] Neither study showed a benefit for chlorhexidine. Older studies have been similarly disappointing.[170] MASCC recommends that chlorhexidine not be used to prevent oral mucositis in patients with solid tumours of the head and neck who are undergoing radiotherapy in their clinical practice guidelines.[56] In addition, Cochrane stated in the most recent update of its' systematic review of prevention of oral mucositis that chlorhexidine has clearly shown no evidence of a benefit compared to either placebo or no treatment.[51] Further study of this agent for mucositis prevention is not warranted without significant changes in formulation. Despite this, chlorhexidine continues to be effectively used for oral cleansing in other situations. Finally, low level laser therapy showed a significant benefit for reducing mucositis severity in two studies, with one study comparing laser to saline and providone-iodine rinses[121], and the other comparing to sham laser therapy.[122] Despite the relatively small number of participants in the two studies, these positive findings warrant further investigation. Low level laser therapy is currently supported in the MASCC Guidelines for prevention of oral mucositis and its associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before HSCT.[56] However, due to the complex nature of the technology and differences in wavelengths used, the guidelines recommend caution, adding that it should be used only if the treatment centre is able to support the necessary technology and training. In the two studies included in the current review, both used the wavelength 632.8 nm and energy between 10 and 25 mW. Studies using

consistent wavelengths and energy, in combination with sham laser for placebo control will improve the level of evidence available for this intervention in the future.

4.2 Implications for Practice

There have been significant resources spent on researching interventions for mucositis in the last two decades, increasing particularly in the last 10 years. Although swaths of agents have been tested, only a handful has shown evidence of benefit, which is ultimately weak in nature. These agents include amifsotine (intravenous administration), aloe vera, G-CSF, honey, sucralfate, morning radiotherapy, providone-iodine and Wobe-Mugos E. The consideration of benefit relates to significant improvement in incidence of severe mucositis (or severity) when aggregated results are assessed statistically by meta-analysis. This approach is somewhat similar to the Cochrane systematic review of interventions for prevention of oral mucositis[51], and not surprisingly has many overlapping findings. The appropriateness of the intervention in a clinical context is not factored in by meta-analysis. Efforts by MASCC to review the literature and develop guidelines for mucositis prevention in the context of clinical practice represents a contrasting approach to dealing with evidence, and does not rely on statistical integration of data to form recommendations.[57] Regardless of the methodological framework utilised in the approach, the fundamental requirement is to assess the body of literature and develop recommendations based on evidence of the highest possible quality.

4.3 Implications for Research

Without well-designed double blind placebo controlled trials, it is difficult to see how improvement in the mucositis prevention knowledge base can significantly advance. The vast majority of studies included in this systematic review lacked adequate controls or blinding, and

recruited too few participants to achieve statistical power. This is a problem throughout mucositis research and likely stems from a lack of funding for supportive care agent trials.

Future clinical trials need to take into consideration the previous systematic reviews assessing mucositis interventions and their findings. For example, there is clear evidence for lack of protective effect with chlorhexidine[51, 56, 62, 63], yet studies continue to be published investigating its effectiveness. This is a waste of resources and effort. In contrast, there are a small number of agents that show some promise to date, but have yet to be investigated in well designed clinical trials. In particular, honey has shown overall benefit for preventing severe oral mucositis in patients treated with radiotherapy for head and neck cancer in three small studies at high risk of bias.[116-118] However, it should also be noted that each study had a different type of honey under investigation and used different mucositis assessment scales. A large multinational clinical trial comparing honey to placebo is now needed to confirm these promising early results and increase the level of evidence available. Until such time, caution is required when considering any recommendation of use of honey for prevention of oral mucositis. Finally, inconsistency in measuring and reporting outcomes was a major hindrance to pooling data for meta-analysis. Leadership by the supportive oncology societies is needed for developing standardised reporting guidelines for all mucositis trials.

4.4 Conclusion

This systematic review has identified a small number of interventions that provide weak evidence of benefit to prevent oral mucositis in head and neck cancer patients treated with radiotherapy, with or without chemotherapy. A lack of repetition studies and consistency in reporting of outcomes prevented aggregation of study results into statistical meta-analysis for most interventions. One intervention that warrants further investigation is honey, as studies to date have shown protection from radiation-induced oral mucositis. However, these studies have

been of low evidence and require confirmation in well designed clinical trials. Future studies should include placebo controls and ensure double blinding to increase the level of evidence available for the few promising interventions. Standardisation of reporting of mucositis intervention trials would improve evaluation of evidence in future systematic reviews.

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Appendix 1 - Clinical appraisal instruments

JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was the assignment to treatment groups truly random?	☐	☐	☐	☐
2. Were participants blinded to treatment allocation?	☐	☐	☐	☐
3. Was allocation to treatment groups concealed from the allocator?	☐	☐	☐	☐
4. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
5. Were those assessing outcomes blind to the treatment allocation?	☐	☐	☐	☐
6. Were the control and treatment groups comparable at entry?	☐	☐	☐	☐
7. Were groups treated identically other than for the named interventions	☐	☐	☐	☐
8. Were outcomes measured in the same way for all groups?	☐	☐	☐	☐
9. Were outcomes measured in a reliable way?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐
	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

		Yes	No	Unclear	Not Applicable
1.	Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2.	Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3.	Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4.	Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5.	Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6.	Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7.	Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8.	Were outcomes measured in a reliable way?	☐	☐	☐	☐
9.	Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	☐	☐	☐	☐
2. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
3. Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
4. Were outcomes assessed using objective criteria?	☐	☐	☐	☐
5. If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

Appendix 2 - Data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer _____ Date _____

Author _____ Year _____

Journal_____ Record Number_____

Study Method

RCT ☐ Quasi-RCT ☐ Longitudinal ☐

Retrospective ☐ Observational ☐ Other ☐

Participants

Setting _____

Population _____

Sample size

Group A _____ Group B _____

Interventions

Intervention A _____

_____

Intervention B _____

_____

Authors Conclusions:

_____

_____

_____

Reviewers Conclusions:

_____

_____

_____

Study results

Dichotomous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Appendix 3 - Detailed search strategies

a. PUBMED

#1. mucositis[tw] or stomatitis[tw] or mucositides[tiab] or stomatitides[tiab] or mucosal injur*[tiab] or mucosal barrier[tiab] or mucosa inflammation[tiab] or mucous membrane[tw]

#2. head and neck neoplasms[tw]

#3. neoplasms[mh] OR neoplasm*[tw] OR cancer*[tw] OR tumour*[tw] OR tumor[tw] OR tumours[tw] OR malignanc*[tw] OR carcino*[tw]

#4. mouth[tw] OR pharynx[tw] OR nasal cavity[tw] OR nasopharynx[tw] OR oropharynx[tw] OR laryngopharynx[tw]

#5. randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trial[tw] OR controlled clinical trial[tw] OR random allocation[tw] OR double-blind method[tw] OR single-blind method[tw] OR clinical trial[pt] OR clinical trials[mh] OR clinical trial[tw] OR research design [mh:noexp] OR comparative study[pt] OR evaluation studies as topic[mh] OR follow-up studies[mh] OR prospective stud*[tw] OR cross over stud*[tw]

#6.Radiation/adverse effects[Mesh] OR Drug therapy/adverse effects[Mesh]

#7. chemotherap*[tw] OR radiotherap*[tw] OR radiation*[tw] OR irradiat*[tw] external beam [tw] OR IMRT[tw] OR cisplatin[nm] OR cetuximab[nm] OR carboplatin[nm] OR paclitaxel[nm] OR fluorouracil[nm]

#8. #1 AND (#2 OR (#3 AND #4)) AND #5 AND #6

#9. #1 AND (#2 OR (#3 AND #4) AND# 7) AND #5

#10. (#1 OR #6) AND (#2 OR (#3 AND #4) AND #5

#11. (#1 OR #6) AND (#2 OR (#3 AND #4) AND #7) AND #5

#12. ((#1 OR #6) AND (#2 OR (#3 AND #4) AND #7))AND #5) NOT review[pt] Limits: Publication Date from 1998/06/01 to 2010/06/01

b. EMBASE

1. exp "head and neck tumor"/

2. (neoplasm$ or cancer$ or tumour$ or tumor$ or malignan$ or carcino$).mp.

3. (radioth$ or radiat$ or irradiat$ or radiochemo$ or chemo$).mp.

4. exp stomatitis/

5. exp mucosa inflammation/

6. (stomatitis or mucositis or (oral and candid$) or (oral adj4 mucositis) or (oral and fung$) or mycosis or mycotic or thrush).mp.

7. (mouth or pharynx or nasal cavity or oropharynx or nasopharynx or laryngopharynx).mp.

8. 2 and 7

9. 1 or 8

10. 3 and 9

11. or/4-6

12. 10 and 11

13. limit 12 to (human and english language and embase and clinical trial and (article or conference abstract or conference paper)

c. CINAHL

S1. TX head and neck neoplasms

S2. (MH "Head and Neck Neoplasms+")

S3. TX clinical trial*

S4. (MH "Clinical Trials+")

S5. TX mucositis OR stomatitis

S6. (MH "Mucositis") or (MH "Stomatitis+")

S7. S5 or S6

S8. S1 or S2

S9. S3 or S4

S10. S7 and S8 and S9

S11. PT clinical tria

S12. S7 and S8 and S11

S13. S9 or S11

S14. S7 and S8 and S13

S15. TX neoplasm* and TX (head OR neck)

S16 S1 or S2 or S15

S17. S7 and S13 and S16

d. CENTRAL

#1 MeSH descriptor Head and Neck Neoplasms explode all trees

#2 (neoplasm* or cancer* or tumour* or tumor* or malignan* or carcino*)

#3 (radioth* or radiat* or irradiat* or radiochemo* or chemo*)

#4 MeSH descriptor Stomatitis explode all trees

#5 MeSH descriptor Mucositis explode all trees

#6 stomatitis or mucositis

#7 (oral near candid*) or (mouth near candid*) or (oral near mucositis) or (oral and fung*) or (mycosis or mycotic or thrush)

#8 (mouth or pharynx or nasal cavity or oropharynx or nasopharynx or laryngopharynx)

#9 (#2 AND #8)

#10 (#1 OR #9)

#11 (#3 AND #10)

#12 (#4 OR #5 OR #6)

#13 (#11 AND #12)

e. Web of Science

#1. TS=(stomatitis OR mucositis) AND Language=(English) Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH Timespan=1998-2010

#2. TS=(cancer* OR tumor* OR tumour* OR neoplasm* OR malignan* OR carcino*) AND Language=(English) Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH Timespan=1998-2010

#3. TS=(head OR neck OR mouth OR oral cavity OR pharynx OR larynx OR nasopharynx OR larayngopharynx OR oropharynx OR nasal cavity) AND Language=(English) Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH Timespan=1998-2010

#4. #3 AND #2 Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH Timespan=1998-2010

#5. TS=(radiat* OR radioth* OR irradiat* OR chemo* or radiochem*) AND Language=(English) Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH Timespan=1998-2010

#6. #5 AND #4 Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH Timespan=1998-2010

#7. #6 AND #1 Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH Timespan=1998-2010

#8. TS=(clinical trial*) AND #7 AND Language=(English) Databases=SCI-EXPANDED, CPCI-S, CPCI-SSH Timespan=1998-2010

Appendix 4 – Included studies

MAStARI

Study	Methods	Participants	Intervention A	Intervention B	Notes
Abbasi Nazari M., Sadrolhefazi B., Nikoofar A., Erfan M., Azizian H., Alamy M., 2007	RCT	Adult patients with cancer in oral cavity, nasopharynx or hypopharynx	10 mL of allopurinol mouthwash 3 times a day for 3 minutes and then discards without swallowing	10 mL of placebo mouthwash 3 times a day for 3 minutes and then discards without swallowing	Reduced incidence of severe oral mucositis in the allopurinol group compared to placebo in weeks 3 - 6.
Adamietz IA, Rahn R, Bottcher HD, Schafer V, Reimer K, Fleischer W, 1998	RCT	Adults receiving radiochemotherapy for treatment of head and neck cancers	Rinsing 4 times daily (3 min each) with 100 ml povidone-iodine solution in addition to daily supportive care regimen (nystatin suspension, 4-5 rinses daily), dexpanthenol(Bepanthen, Roche tablets, 4 x 1 tablet daily), rutosides (4 x 1 tablet daily) and immunoglobulins (one i.m. injection weekly).	Rinsing 3 times daily with sterile water in addition to daily supportive care regimen (nystatin suspension, 4-5 rinses daily), dexpanthenol(Bepanthen, Roche tablets, 4 x 1 tablet daily), rutosides (4 x 1 tablet daily) and immunoglobulins (one i.m. injection weekly).	Incidence and duration of severe oral mucositis is decreased by povidone-iodine rinses compared to sterile water.
Anne PR, Machtay M, Rosenthal DI, Brizel DM, Morrison WH, Irwin DH, et al., 2007	RCT	Phase II, open-label, single-arm, multicenter trial recruited adult head and neck cancer patients receiving radiotherapy alone.	sucutaneous amifostine		Subcutaneous amifostine (500 mg) did not reduce incidence of severe oral mucositis
Antonadou D, Pepelassi M, Synodinou M, Puglisi M, Throuvalas N., 2002	RCT	Adult patients with histologically proven squamous cell carcinoma of the head and neck receiving radiochemotherapy	Intravenous amiifostine (300 mg/m2)	Nothing	Amifostine reduced the incidence of grade 4 oral mucositis (but not when considering grade 3+)
Arun Maiya, G, Sagar MS, Fernandes D., 2006	RCT	patients with carcinoma of oral cavity with stages II-IV a being uniformly treated with curative total tumour dose of 66 Gy in 33 fractions over 6 wk	He-Ne laser (wavelength 632.8 nm and output of 10 mW) given intra-orally outside the malignant tumour located area, three minutes for five days a week till the completion	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 rank in study group showed significant decrease (P<0.001) as compared to control group (Table). Mean pain score in

			of radiotherapy. The treatment time (t) for each application point was given by equation t(sec) = energy (J/cm2) x surface area (cm2)/Power (W). The average energy density of 1.8 J/cm2 was delivered to the treatment area.		study group showed significant decrease in the mean pain score (2.6 ± 0.64) as compared to control group (6.68 ± 1.44) (P<0.001). At the end of radiotherapy, the mucositis grade was significantly (P<0.001) lower in the study group than in control group. Mucositis grade was 1.72 ± 0.67 in the study group and 3.32 ± 0.69 in control group. High risk of bias as neither patients nor investigators blinded.
Bennett CL, Lane D, Stinson T, Glatzel M, Buntzel J., 2001	RCT	patients had stage III or IV squamous cell carcinoma of the head and neck region. therapy consisted of surgical tumor excision followed by adjuvant radiochemotherapy (carboplatin), or primary radiochemotherapy in patients with inoperable tumours	Amifostine (i.v.) rapid infusion 500 mg	Nothing	amifostine was effective at preventing severe oral mucositis.
Bensadoun RJ, Franquin JC, Ciais G, Darcourt V, Schubert MM, Viot M, et al., 1999	RCT	patients with carcinoma of the oropharynx,hypopharynx and oral cavity being treated by external radiotherapy (without prior surgery or concommitant chemotherapy)	Low level laser therapy (He-Ne) 60 mW, wavelength 632.8 nm. 2 J/cm2 applied at nine intraoral points, equally distributed on the treated surfaces, for 33 s per point.	sham laser	LLLT modestly but consistantly reduced oral mucositis severity and pain across duration of radiotherapy
Bentzen SA, Saunders MI, Dische S, Bond SJ., 2001	RCT	Patients more than 18 years of age with squamous cell carcinoma in the main sites within the head and neck region	CHART was delivered with 1.5 Gy per fraction, 3 fractions a day, on 12 consecutive days including the weekend. The prescribed interfraction interval of 6 h was strictly adhered to. The large volume received 37.5 Gy in 25 fractions, and	Conventional fractionation was delivered as 44 Gy in 22 fractions to the large volume and 22 Gy in 11 fractions to the small volume. Thus, a total dose of 66 Gy was delivered with 2 Gy per fraction, 1 fraction per day, 5 days a	Reduced incidence of confluent oral mucositis in conventional arm compared to hyperfractionated radiotherapy arm. The peak prevalence of confluent mucositis after CHART was 60% (95% CI (56, 64)%) and this was seen at

			the small volume received 16.5 Gy in 11 fractions which gave a total dose of 54 Gy in 36 fractions	week	the end of the third week after the start of radiotherapy. The incidence of con¯uent mucositis after CHART was 75% (95% CI (71, 79)%). In the conventional arm, the peak prevalence of confluent mucositis was 34% (95% CI (29, 39)%) and this was seen at the end of week 6 after the start of radiotherapy. The incidence of confluent mucositis in the conventional arm was 44% (95% CI (39, 49)%).
Biswal BM, Zakaria A, Ahmad NM., 2003	RCT	Patients receiving conventional fractioned radiotherapy to the head or neck (age range 14 - 89)	Patients were asked to take 20 ml of natural honey before radiotherapy, 20 ml after radiotherapy and 20 ml 6 h after therapy. They were advised to rinse honey on the oral mucosa and then to swallow slowly to smear it on the oral and pharyngeal mucosa.	Nothing	Honey significantly reduced the incidence of severe mucositis in the treatment group compared to the control group.
Bjarnason GA, MacKenzie RG, Nabid A, Hodson ID, El-Sayed S, Grimard L, et al., 2009	RCT	Patients with squamous cell carcinoma of the oral cavity, pharynx, or larynx, eligible to receive RT without chemotherapy	Morning radiotherapy (8 - 10 am) once daily fractionation schedule, dose 50 - 70 Gy. In addition to standardised supportive care protocol consisting of a dilute solution of sodium bicarbonate to rinse the mouth every 2 h. If Grade 2 mucositis was observed, a mouthwash containing diphenhydramine, tetracycline, and nystatin was used every 4-6 h. Nonsteroidal anti-inflammatory drugs were	Afternoon radiotherapy (4 - 6 pm) once daily fractionation schedule, dose 50 - 70 Gy. In addition to standardised supportive care protocol consisting of a dilute solution of sodium bicarbonate to rinse the mouth every 2 h. If Grade 2 mucositis was observed, a mouthwash containing diphenhydramine, tetracycline, and nystatin was used every 4-6 h. Nonsteroidal anti-inflammatory drugs were	There was no significant difference between arms for incidence, severity or duration of oral mucositis. Subgroup analysis suggests some protection against severe oral mucositis with morning radiotherapy when dose is 66 - 70 Gy delivered in 33 - 35 fractions.

			allowed, but a mouthwash containing steroids was not. Xylocaine gel or Xylocaine viscous was allowed for painful oral ulcerations	allowed, but a mouthwash containing steroids was not. Xylocaine gel or Xylocaine viscous was allowed for painful oral ulcerations	
Bourhis J, De Crevoisier R, Abdulkarim B, Deutsch E, Lusinchi A, Luboinski B, et al., 2000	RCT	patients with an inoperable nonmetastatic Stage IV HNSCC were entered in this study. treatment consisted of very accelerated radiotherapy given 64 Gy in 3.5 weeks	150 mg/m2, amifostine administered IV twice daily	Nothing	i.v. amifostine significantly reduced incidence of grade 4 mucositis (increased grade 3), and reduced duration of severe mucositis
Braaksma M, Van Agthoven M, Nijdam W, Uyl-De Groot C, Levendag P., 2005	RCT (cost analysis)	patients were treated with 4 weekly courses of paclitaxel 60 mg/m2 intravenously (iv), concomitant with external beam radiation (46 Gy to primary tumour and bilateral neck nodes [18]). After 46 Gy a booster dose of 26 Gy was applied to the primary tumour (and positive neck nodes).	500 mg amifostine s.c. 15-30 min prior to each fraction	nothing	Subcutaneous amifostine was not effective at preventing mucositis. Amifostine was discontinued due to toxicity in 5 patients
Brizel DM, Murphy BA, Rosenthal DI, Pandya KJ, Glueck S, Brizel HE, et al., 2008	RCT (phase II clinical trial)	Adults with newly diagnosed stage III/IVa or IVb squamous carcinoma of the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx undergoing curative-intent CRT were eligible	Palifermin (Kepivance; Amgen Inc, Thousand Oaks, CA) 60 g/kg or matching placebo was administered by intravenous bolus injection on Friday (study day 1) before the first week of CRT. Subsequent doses were administered for 7 consecutive weeks, on each Friday after completion of weekly radiation treatment. Two additional doses were given on weeks 8 and 9.	placebo (not defined)	Overal palifermin was not effective at reducing oral mucositis. However, subgroup analysis of patients treated with hyperfractionated radiotherapy showed some benefit.
Brizel DM, Wasserman TH, Henke M, Strnad V, Rudat V, Monnier A, et al., 2000	RCT	Patients with newly diagnosed, previously untreated squamous cell head and neck	Amifostine was delivered 15 to 30 minutes before radiotherapy daily as a 3-	Nothing	Amifostine (i.v.) did not improve incidence or severity of oral mucositis in this study.

		cancer, to receive definitive irradiation to a total dose of 66 to 70 Gy. Doses of postoperative irradiation were either 60 to 64 Gy (high-risk patients) or 50 to 54 Gy (low-risk patients).	minute intravenous (IV) infusion at a dose of 200 mg/m2 dissolved in normal saline at a concentration of 1 mg/mL		
Buentzel J, Micke O, Adamietz IA, Monnier A, Glatzel M, De Vries A., 2006	RCT	adult patients scheduled for definitive or adjuvant chemoradiotherapy (carboplatin and standard fractionated radiotherapy) for histologically confirmed squamous-cell carcinoma of the head and neck	Days 1 to 5 and Days 21 to 25, patients received amifostine at 300 mg/m2. Days 6 to 20 and Days 26 to 30/35, patients received amifostine at 200 mg/m2	equivalent volume placebo (mannitol)	amifostine (i.v.) is not effective for preventing oral mucositis. Significantly increased toxicity in the amifostine arm
Buntzel J, Kuttner K, Frohlich D, Glatzel M., 1998	RCT	stage III or IV carcinoma of the head and neck, age between 16 and 80 years, hosptialised for duration of study (6 weeks). Treated with radiotherapy and carboplatin as adjvant or definitive therapy.	500 mg amifostine rapid intravenous infustion on days of carboplatin (days 1 -5 and 20 - 25)	nothing	Amifostine prevented severe mucositis caused by standard fraction radiotherapy and carboplatin. This paper includes patients from previously published work (Buntzel 1998 Support Care Cancer)
Buntzel J, Riesenbeck D, Glatzel M, Berndt-Skorka R, Riedel T, Mucke R, et al., 2010	RCT	patients with squamous cell carcinoma of the head and neck region with deficiency in selenium and planned radiation field including 75% of the major salivary glands. Radiation to primary tumour and lyphatic neck at standard fractionation.	500 microgram sodium selenite two days before starting radiotherapy and then 500 ?g selenite on the days of radiotherapy. During weekends and official holidays, only 300 microgram selenite were given. Sodium selenite was taken as an oral fluid one hour before the radiotherapy was performed	nothing	Selenium was not effective at preventing mucositis. Showed a trend towards worse mean mucositis score at week 5 compared to controls (not significant).
Carter DL, Hebert ME, Smink K, Leopold KA, Clough RL, Brizel DM., 1999	RCT	Adult patients undergoing curative intent RT for primary squamous cell carcinoma of	swish 15 ml (1 gm) of sucralfate suspension for at least 2 minutes and then	swish 15 ml placebo for at least 2 minutes and then swallow four times daily	Sucralfate did not significantly reduce severe mucositis compared to placebo

		the oral cavity, oropharynx, hypopharynx, nasopharynx, or larynx (mixed population with concurrent chemo, frationation schedules, and tumour stage)	swallow four times daily throughout the entire course of treatment	throughout the entire course of treatment	
Cengiz M, Ozyar E, Ozturk D, Akyol F, Atahan IL, Hayran M., 1999	RCT	adult patients with head and neck cancer recieving radiotherapy	6 g sucralfate suspension as mouth wash in four divided doses orally before meals and bed time	placebo mouth mouth	Sucralfate treatment prevented severe mucositis. More patients had low grade mucositis in the sucralfate group compared to control group.
Cerchietti LCA, Navigante AH, Lutteral MA, Castro MA, Kirchuk R, Bonomi M, et al., 2006	RCT	Adults patients with squamous head and neck cancer, clinically unresectable tumor, committed to a treatment of induction chemotherapy (cisplatin + 5-FU) plus CRT (BID Rx and cisplatin + 5-FU)	L-alanyl-L-glutamine 0.4 g/kg weight/day (2 mL/kg weight/day) diluted in normal saline (1:5 v/v) administered by intravenous infusion of 4 h on the same days as the chemotherapy	placebo (normal saline)	Intravenous glutamine was effective at reducing mean mucositis score and incidence of severe mucositis
Dorr W, Herrmann T., 2007	RCT	Patients with head and neck cancer receiving radiotherapy	Drug treatment started 3 days before and lasted until 5 days after the last radiation fraction (up to 8 weeks) administered orally, 3 × 4 tablets per day. The verum (Wobe-Mugos® E) contained papain 100 mg, trypsin 40 mg, and chymotrypsin 40 mg. Additives were: lactose, macrogol 6000, co-polyvidone, magnesium stearate, polyvidone, talcum, methacrylic acid, co-polymerisate type A, shellac, dibutyl phthalate and odourantia.	identical placebo tablet contained ludipress, corn starch, magnesium stearate, cellulose, mikri, silicic acid, Capol 600, saccharose, talcum, vanilline, calcium carbonate, titanium dioxide, soluble polyvinylpyrrolidone, white clay, Pek 6000, isopropanol, Eudragit® L 12,5 P	Wobe-Mugos was not effective at reducing mucositis severity, incidence or duration
El-Sayed S, Nabid A, Shelley W, Hay J, Balogh J, Gelinas M, et al., 2002	RCT	Patients with histologically confirmed nonmetastatic carcinoma of the oral cavity,	BCoG (containing bacitracin, clotrimazole, and gentamicin) lozenge (one lozenge qid, day	placebo lozenge	The BCoG lozenge did not improve mucositis. OMAS scoring was used

		pharynx (nasopharynx, oropharynx, or hypopharynx), or larynx to receive radical or postoperative radiotherapy	1 to end of radiotherapy)		
Emami H, Jalilian M, Parvizi A, Amouheidari A., 2008	RCT	Patients receiving at least 40 Gy radiations to at least two or more sites of oropharynx, oral cavity, soft or hard palate, hypopharynx, and nasopharynx, entered the study. All the patients were treated with conventional radiotherapy, 2Gy/fraction, one fraction per day and five fractions per week to a total dose of 55-60 Gy.	Sucralfate suspensions were administered from the beginning of radiation therapy (15cc of 10% suspension: 10mg/100cc, 4 times a day mouthwash).	stated as placebo but not defined	Significantly reduced mean grade of mucositis and reduced frequency of severe mucsitis, however only measured up to week 4.
Epstein JB, Silverman S, Paggiarino DA, Crockett S, Schubert MM, Senzer NN, et al., 2001	RCT	Male and nonpregnant female subjects 18-80 years old with diagnoses of head and neck carcinoma who were scheduled to receive a total external beam RT dose of at least 5000 cGy via a megavoltage treatment with either a cobalt-60 teletherapy unit or a linear accelerator	0.15% benzydamine oral rinse (1.5 mg/mL benzydamine) (vehicle included approximately 10% alcohol by volume, menthol, peppermint oil, clove oil, and other flavoring agents). Subjects were to rinse with 15 mL for 2 minutes, 4-8 times daily before and during RT, and for 2 weeks after completion of RT.	Placebo identical in flavour and appearance	Reduced area under the curve mucositis severity. The scale used to measure was study-specific, and no incidence data was presented.
Ertekin MV, Koc M, Karslioglu I, Sezen O., 2004	RCT	Thirty adult patients with histologically proven cancer of the head and neck who were to receive curative RT or chemoradiotherapy	Zinc sulfate (containing 50 mg zinc; Zinco 220 capsule, Berko Ilac¸ Istanbul)three times daily at 8-hour intervals from the first day of RT, during RT and for 6 weeks after treatment, including weekends	empty placebo capsules	Zinc sulfate prevented grade 3 mucositis compared to placebo and reduced duration of mucositis.
Escribano A, Garcia-Grande A, Montanes P, Miralles L, Garcia A., 2002	Case series	Adults with head and neck malignant tumours, receiving adjuvant radiotherapy or	Aerosol orgotein (8 mg in 4 ml) administered just before each radiotherapy session		Incidence of grade 3 mucositis is 33% in this cohort, which is similar to studies in patients

		chemoradiation with curative intent			treated with comparable Rx. The table of results does not match the text reported for mucositis incidence
Etiz D, Erkal HS, Serin M, Kucuk B, Hepari A, Elhan AH, et al., 2000	RCT	Patients with histopathologically confirmed head and neck malignancies necessitating radiation therapy with portals covering at least one-third of the oral mucosa	six daily doses of sucralfate oral suspensions at regular intervals in measures of 1 g, starting on the day of the first radiation therapy fraction and continuing throughout the scheduled radiation therapy course including weekends.	identical placebo suspension	Mucositis severity was less in the sucralfate arm. No incidence data was presented. The mucositis was scored by a method suggested by Van der Schueren 1990, not a validated system
Evensen JF, Bjordal K, Jacobsen AB, Lokkevik E, Tausjo JE., 2001	RCT	adults with squamous cell carcinoma of the head and neck region receiving standard fractionated radiotherapy.	Starting day 1 of radiotherapy,participants performed oral rinsing 5 times a day, lasting for at least 2 min, before spitting out the Na-SOS suspension	Placebo administered identically	Figures indicate that more patients treated with SOS had grade 4 mucositis compared to placebo. Used mucositis scoring system of Van der Schueren (out of 4, but not a validated system)
Ferreira PR, Fleck JF, Diehl A, Barletta D, Braga-Filho A, Barletta A, et al., 2004	RCT	Patients with a confirmed histologic diagnosis of cancer of the oral cavity and oropharynx referred to definitive or adjuvant radiotherapy dcelivered as standard fractionations	500 mg vitamin E (oil in capsule). Patients were taught to dissolve it in saliva, rinse it all over the oral cavity for 5 minutes, and then swallow it immediately before every session of irradiation, Monday through Friday, from the first to the last day of RT. A second capsule was similarly administered at the patient's home after 8 to 12 hours.	500 mg placebo (evening primrose oil) administed in an identical manner	measured "symptomatic mucositis" which is grade 2 or higher by RTOG scale. Vitamin E group had significantly less symptomatic mucositis than the placebo group (21.6% vs 33.5%).
Goyal M, Shukla P, Gupta D, Bisht SS, Dhawan A, Gupta S, et al., 2009	RCT	patients with histologically confirmed non-metastatic carcinoma of the oral cavity, pharynx (nasopharynx, oropharynx or hypopharynx), or larynx receiving external	morning radiotherapy	evening radiotherapy	Incidence of severe mucositis was higher in the evening radiotherapy group

		beam radiotherapy with curative intent (standard fractionations)			
Gujral MS, Patnaik PM, Kaul R, Parikh HK, Conradt C, Tamhankar CP, et al., 2001	RCT	Biopsy proven squamous cell carcinoma of the head or neck scheduled to recieve standard daily fractions up to maximum 70 Gy.	Wobe-Mugos E (containing papain 100 mg, trypsin 40 mg, chymotrypsin 40 mg), 3 tablets 3 times a day, 3 days prior to starting radiotherapy until 5 days after completion	nothing	Wobe-Mugos E group had significantly less severe mucositis compared to control group.
Huang EY, Leung SW, Wang CJ, Chen HC, Sun LM, Fang FM, et al., 2000	RCT (pilot)	patients with head and neck cancer receiving primary or adjuvant irradiation (1.8 Gy/fraction, 5 fractions per week)	glutamine (Glutamine 16 g in 240 ml normal saline was prepared for suspension in a plastic bottle. The solution was stored in the refrigerator; shaking the bottle before administration was mandatory. Patients swished 30 ml test solution for 3 minutes and expectorated before meals and at bedtime daily. The rinse was commenced on the morning of the first fraction of radiotherapy and completed at bedtime of the twenty-fifth fraction of radiotherapy)	saline administered in same manner	Small study showing possible benefit of oral glutamine in patients treated with radiotherapy. Prevented grade 3+ oral mucositis entirely. However pain medication usage was not different between groups.
Johnson DJ, Scott CB, Marks JE, Seay TE, Atkins JN, Berk LB, et al., 2002	Single arm phase II study	patients with head and neck cancer receiving radiotherapy (2 Gy/day - up to 60-70 Gy) postoperatively or definitively	misoprostol swished and swallowed. Each dose was prepared by crushing one tablet (200 g) into a dose cup, adding 15 mL of purified or distilled water and stirring thoroughly for approximately 5 min before administration. Administered daily throughout radiation therapy before each session.		Higher than expected incidence of severe mucositis in this cohort. 55% experienced grade 3 or 4 OM (RTOG). misoprostol delivered in this manner did not protect the mucosa for this group of patients and may have contributed to increased toxicity.
Karacetin D, Yucel B,	RCT (non-placebo)	Head and neck cancer	short infusion (15 min)	nothing	Incidence and severity of

Leblebicioglu B, Aksakal O, Maral O, Incekara O., 2004		patients with local and/or regional disease treated with radiotherapy (2 Gy/fraction, 5 fractions/week)	amifostine (210 mg/m2) administered 20 mins before each radiotherapy session		mucositis was the same across the two groups
Kaul R, Mishra BK, Sutradar P, Choudhary V, Gujral MS., 1999	RCT	Head and neck carcinoma patients treated with conventional fractionation RT (50 - 60 Gy delivered in 5 - 6 weeks) [unclear if surgery was completed, baseline patient data not included]	Wobe-Mugos 3 tablets, 3/day, beginning 3 days before RT until 1 week following completion of RT	nothing	Study found a small decrease in incidence of severe OM in group treated with Wobe-Mugos. However, the results are at high risk of bias since the patient demographics are not described, and co-medication may have been a factor.
Kazemian A, Kamian S, Aghili M, Hashemi F, Haddad P., 2009	Double blind placebo controlled RCT	Head and neck cancer patients treated with standard fractionation radiotherapy. Roughly a third of patients also received concurrent chemotherapy	0.15% benzydamine oral rinse. 15 mL for 2 min, 4 times a day from the first day of RT to the end of the treatment	identical placebo made of the vehicle only, administered in the same fashion	Benzydamine rinse appears to decrease the incidence of severe mucositis, as well as reduce the mean severity of mucositis in head and neck cancer patients
Cheng KK, Yuen KJ. , 2006	RCT (pilot, active control)	head and neck cancer patients scheduled to receive standard fraction radiotherapy	0.15% wt/vol benzydamine hydrochloride starting on the first day of radiotherapy and continuing until 2 weeks after completion. Mouth rinsing was completed in the early morning and at bedtime.	0.2% wt/vol chlorhexidine gluconate administered in the identical manner	Very small study of only 14 patients. Benzydamine showed some benefit over chlorhexidine in reducing the incidence of severe mucositis.
Koukourakis MI, Kyrias G, Kakolyris S, Kouroussis C, Frangiadaki C, Giatromanolaki A, et al., 2000	RCT (phase II)	head and neck cancer patients with local or regional disease treated by radiotherapy	subcutneous amifostine (500 mg) administered 20 mins before each radiotherapy session	nothing	subcutaneous amifostine appears to be safe and effective at reducing oral mucosal toxicity in this patient cohort by preventing severe mucosiitis
Lanzos I, Herrera D, Santos S, O'Connor A, Pena C, Lanzos E, et al., 2010	RCT	paients with head-and-neck carcinoma (most of them squamous cell carcinomas),	Perio-Aid Tratamiento® (Dentaid, Cerdanyola del Valles, Spain) composed of	identical placebo	Tested mouth rinse did not improve mucositis scores compared to placebo. Analysis

		and their oncology therapy included normal fractioned radiation in doses ranging from 50-80 Gy	0.12% CHX and 0.05% CPC as active ingredients. Rinse 15 ml twice a day		of mucositis was presented as "increased", "decreased" or "no change". No usable data for metaanalysis.
Leborgne JH, Leborgne F, Zubizarreta E, Ortega B, Mezzera J., 1998	RCT	All patients with previously untreated squamous cell carcinoma of the head and neck who were candidates for radical radiation therapy were included. The tumour dose per fraction was 1.6 Gy twice daily with a 6 h interfraction interval and all fields were treated each day, 5 days a week.	single daily dose of 40 mg oral prednisone starting on day 8 from the beginning of treatment through day 28. From day 29 through day 33 the prednisone dose was tapered to 20 mg daily and from day 34 through day 43 to 20 mg every other day.	placebo as identical capsules	A non-significant reduction in treatment delays was seen in the prednisone group. No significant difference in mucositis incidence, duration or severity stated, however no data presented.
Lievens Y, Haustermans K, Van den Weyngaert D, Van den Bogaert W, Scalliet P, Hutsebaut L, et al., 1998	RCT	patients with malignancy of the oral cavity, the oropharynx, the larynx or the hypopharynx, treated with standard fraction radiotherapy.	Sucralfate prepared as an oral suspension, identical in taste and consistency. Patients were instructed to take the suspension six times a day in doses of 1 g with regular intervals. The oral intake (mouth washings and swallowing) was started on the morning of the first radiotherapy session and continued during the whole radiation treatment.	Identical taste placebo	Sucralfate did not significantly improve mucositis compared placebo over the course of radiation. Mean (SD) scores were sucralfate 3.3 ± 2.0, placebo 2.6 ± 1.7 (grading system 0 -6, study specific). Poor compliance in the sucralfate arm was caused by complaints of gastrointestinal upset.
Lin LC, Que J, Lin LK, Lin FC., 2006	RCT	Head and neck cancer patients treated by radiotherapy (nearly half also received concurrent chemotherapy which was balanced across groups)	oral zinc (25 mg Pro-Z; Banner Pharmacaps, High Point, NC). Pro-Z is a powder extracted from bovine prostate, which is then chelated to zinc. Patients took three capsules per day, from the first day to the last day of radiotherapy, including weekends and radiotherapy disruptions.	placebo (soybean oil), administered in identical manner	Patients in the zinc arm had significantly lower mean mucositis scores throughout radiation course, and lower incidence of grade 3 mucositis. Subsequent subgroup analysis (published 2010) found that protection was limited to patients with oral cavity cancer

[0], Madan K P, Sequeira P, Shenoy K, Shetty J., 2008	RCT	head and neck cancer patients scheduled to receive standard fraction radiotherapy (adjuvant or definitive)	0.12% chlorhexidine 1% Povidone iodine Salt/sodium bicarbonate Swish 10 ml of mouthwash twice a day for 6 weeks	plain water	Of the three mouth washes tested (and compared to water), povidone iodine was the most effective at reducing severity of mucositis. In addition, povidone iodine delayed the onset of visible mucositis.
Makkonen TA, Minn H, Jekunen A, Vilja P, Tuominen J, Joensuu H, 2000	RCT	patients with head and neck cancer scheduled to receive standard or hyperfractionated radiotherapy (stratified prior to randomisation), as neoadjuvant, adjuvant or definitive treatment	After the cumulative dose of 10 Gy, molgramostim (GMCSF, Leucomax, Schering-Plough Corporation, Espoo, Finland) was started, and 150 to 300 mg (based on bodyweight <70> kg) was given s.c. each day of radiotherapy until the last day of irradiation. Patients also used sucralfate suspension 1 g, 6 times daily orally (Antepsin, Orion Corporation, Orion-Farmos Pharmaceuticals, Turku, Finland). The patient was requested to rinse his or her mouth with the suspension for at least 1 minute before swallowing. Mouth washings were started after the first week of radiotherapy and continued during the entire course of the therapy, including the weekends and other possible breaks.	sucralfate only	No significant difference between the frequency or severity of mucositis between groups. Used a study specific scoring system for mucositis graded 0 - 2.
Mascarin M, Franchin G, Minatel E, Gobitti C, Talamini R, De Maria D, et al., 1999	non-randomised clinical trial	patients with histologic diagnosis of head and neck neoplasm, stages III and IV, treated with hyperfractionated Rx protocol (2 fractions per	G-CSF (3 mg/kg) administered daily by subcutaneous injection, starting on the ®rst day of RT, and given 5 days per week throughout RT	sucralfate and sodium-bicarbonate mouth rinsing	The G-CSF group had a reduced incidence of severe (grade 2+) mucositis for at least weeks compared to the control group. However, the

		day, 5 days/week)	treatment. In addition sucralfate and sodium-bicarbonate mouth rinsing was prescribed		mean mucositis severity and mean onset of maximal mucositis was similar between groups. There was a signigicant reduction in the number of treatment breaks in the G-CSF arm. The is study is non-randomised consecutive patients and non-blinded, as such at a very high risk of bias.
Matceyevsky D, Yaal-Hahoshen N, Vexler A, Asna N, Khafif A, Ben-Yosef R., 2007	non-randomised clinical trial	Patients with head or neck tumours scheduled to receive standard fractionation radiotherapy as primary or post-operative treatment, with or without chemotherapy (carboplatin or cisplatin)	mouthwash solution, LemonR, three times daily starting 1 week before, during, and up to 2 weeks after the completion of radiotherapy. Active ingredients: Dead Sea salt, chamomile extract (Anthemis nobilis), thyme oil (Thymus vulgaris), lemon peel oil (Citrus medica limonum), Clary sage oil (Salvia sclarea) and peppermint oil (Salvia sclare)	baking soda mixed with water or salty water for mucositis	No statistically significant difference between the two groups in respect to incidence of mucositis or incidence of severe mucositis. However, product appears to reduced grade 3/4 mucositis. There was significantly fewer patients requiring treatment breaks in the dead sea product arm. Baseline characteristics of groups suggests control group were at higher risk of oral mucositis although no statistical analysis carried out. Any results are at a high risk of bias
McAleese JJ, Bishop KM, A'Hern R, Henk JM., 2006	RCT	Patients treated by radiotherapy for early glottic carcinoma (once-daily fractions of 3.125 Gy were delivered to a total dose of 50 Gy in 16 fractions in 21 days)	GM-CSF was administered at a dose of 150 mg by subcutaneous injection once daily for 14 days, beginning at the end of the second week of radiotherapy (patients mostly had grade 1 mucositis already)	nothing	No statistical difference between groups in incidence of mucositis or duration. However, there was significantly higher proportion of patients with a maximum mucositis score of 1 in the GM-CSF group compared to controls.
Motallebnejad M, Akram S,	RCT	patients with cancer of the	20 ml pure natural honey 15	20 ml of normal saline (0.09%)	Authors present results

Moghadamnia A, Moulana Z, Omidi S., 2008		head or neck scheduled to receive standard fractionated radiotherapy	minutes before then 20 ml doses again at 15 minutes and six hours after radiotherapy. Patients were instructed to rinse the honey around in their mouths and swallow gradually in order to coat the oral and pharyngeal mucosa.	rinse before and after each radiotherapy session	showing the median OMAS score was increased in the control group over the course of radiotherapy compared to the honey group. No raw data was presented in the text.
Nicolatou-Galitis O, Velegraki A, Sotiropoulou-Lontou A, Dardoufas K, Kouloulias V, Kyprianou K, et al., 2006	non-randomised clinical trial	patients with malignant head and neck tumor, eligible to receive radiotherapy. Patients were treated by either definitive or postoperative radiotherapy, with or without concurrent cisplatin or 5-FU.	fluconazole, 100 mg/day, administered per os, after lunch, from the initiation to the completion of RT (prophylactic group)	fluconazole, 100 mg/day, administered per os, after lunch, upon the development of candidiasis, for 1 week. Upon recurrence of candidiasis, fluconazole was re-administered for another 1 week (therapeutic group)	The incidence of severe mucositis and the onset of mucositis was similar between groups. The incidence of severe mucositis at the end of radiotherapy was significantly higher in the therapeutic group, as was the number of patients requiring treatment interruption due to severe mucositis.
Penpattanagul S., 2007	RCT	Head and neck cancer patients with locally advanced disease, e.g. nasopharyngeal carcinoma (NPC) of stage III or IV who had previously received neoadjuvant chemotherapy. Adjuvant radiotherapy was delivered as conventional fractionation, with concurrent cisplatin chemotherapy.	WF10 therapy at 0.5 mL/kg body weight per day, diluted in 500 mL 5% dextrose water (5% D/W), administered by intravenous infusion over a period of 4 hours for 5 consecutive days, after radiation fractions and repeat the treatment every 3 weeks for 3 cycles, i.e. treatment cycles were administered from Days 1 to 5 in Weeks 1, 4 and 7.	nothing	Not blinded in any way so high risk of bias. At Week 7, 3 control patients had developed grade 2, and 2 patients had developed grade 3 oral mucositis (it is assumed the remaining 2 patients had grade 1 mucositis but this was not stated), whereas, in the WF10 group 5 patients displayed grade 0-1 and only 1 patient displayed grade 2 oral mucositis.
Puataweepong P, Dhanachai M, Dangprasert S, Sithatani C, Sawangsilp T, Narkwong L, et al., 2009	RCT	patients with histological confirmed stage II-IV M0 malignancies of head and neck scheduled to receive conventional radiation in adjuvant or definitive setting	15 mL of Aloe vera juice (consisting of 80% aloe juice, 0.2% preservative, 0.001 % lemon-lime flavor, and sweetened with sorbitol) three times daily, beginning on the	placebo solution was taste-matched, with identical astringency,consistency, and ingredients, but the Aloe vera juice was replaced with water	Significantly more patients experienced severe mucositis in the placebo group compared to the aloe vera group. Duration to the onset of severe mucositis was not

			first day and continuing throughout the three-four weeks of the radiation course and continuing to the end of the 8th week follow-up		different between groups.
Putwatana P, Sanmanowong P, Oonprasertpong L, Junda T, Pitiporn S, Narkwong L., 2009	RCT	patients 18 years and older, diagnosed with head and/or neck cancer, planning to receive conventional fractionation radiation alone or in combination with other treatment (surgery or chemotherapy)	glycerin payayor 2 drops 3 to 5 times a day start and finish day not stated)	benzydamine hydrochloride (Diflam) 15 ml mouth rinsing 3 times a day (start and finish day not stated)	Mean mucositis severity scores were lower in the payayor group. The payayor group also had significantly fewer patients requiring radiation treatment interuption compared to the benzydamine group.
Rashad UM, Al-Gezawy SM, El-Gezawy E, Azzaz AN., 2009	RCT	patients with histologically confirmed, nonmetastatic carcinoma of the oral cavity, pharynx (nasopharynx, oropharynx or hypopharynx) or larynx scheduled to receive standard fractionated radiotherapy and cisplatin concurrent chemotherpay	smear the inside their mouth with 20 ml of pure honey, 15 minutes before, 15 minutes after and 6 hours after radiation therapy	nothing	Incidence of severe mucositis was greater in the control group compared to the honey group. The number of treatment breaks was also higher in the control group.
Saarilahti K, Kajanti M, Joensuu T, Kouri M, Joensuu H., 2002	RCT	patients scheduled to receive postoperative RT for head-and-neck cancer delivered as standard fractions.	GM-CSF mouthwash solution (150 g of dry drug powder into 100 mL of sterile water), delivered 4 times per day (not on weekends), so dose per wash was approximately 37.5 ug in 25 ml. Patients rinsed with the drug solution for 3 min and, after rinsing, swallowed the solution. Rinsing started at the end of the first week of radiation and continued until the last day of therapy.	sucralfate mouthwash solution was prepared by dissolving 4.0 g of sucralfate in 100 mL of sterile water. Dose was split into 4 x 25 ml to be identical to the other treatment group.	mucositis scores tended to be less severe in the GM-CSF-group (p 0.072) with most noticeable difference occurring at week 6 of treatment. Reported pain severity was slightly less in the GM-CSF group, however use of pain medication was similar across groups. No incidence data presented
Sarkar SK, Patra NB, Goswami J, Basu S., 2008	RCT	patients with biopsy proven carcinoma of the head and	weekly concomitant chemotherapy with 40 mg/m2	weekly concomitant chemotherapy with 6 mg/m2	More patients in the cisplatin arm had grade 3 mucositis,

		neck, of stage III or IV(non-metastatic) scheduled to receive standard fractionation radiotherapy with concurrent chemotherapy	cisplatin via intravenous (IV) infusion (as a radiosensitizer in addition to 66 Gy RT in 33 fractions)	vinorelbine via slow IV injection (as a radiosensitizer in addition to 66 Gy RT in 33 fractions)	although difference between groups was not statistically significant.
Scarantino CW, LeVeque F, Swann RS, White R, Schulsinger A, Hodson DI, et al., 2006	RCT	patients with a diagnosis of primarily oral and oropharyngeal squamous cell carcinoma	5 mg of pilocarpine four times daily (start and finish date unclear)	placebo	Incidence of any mucositis and severe (grade 2+) mucositis was similar across both groups.
Schneider SB, Nishimura RD, Zimmerman RP, Tran L, Shiplacoff J, Tormey M, et al., 1999	RCT	patients with histologically proven malignancy of the head or neck region scheduled to receive standard fractionation radiotherapy	subcutaneous G-CSF injections daily throughout RT (between 3 and 12 ug/kg/day, titrated per patient)	placebo injection	Very small study. Trial was not completed, only 14 of a planned 54 were recruited. All patents experienced mucositis as stated by authors. Incidence of severe mucositis was significantly lower in the G-CSF group.
Sprinzl G, Galvan O, de Vries A, Ulmer H, Gunkel A, Lukas P, Thumfart W., 2001	RCT	previously untreated patients with advanced carcinoma (stage III, IV) of the oral cavity, oro- and hypopharynx scheduled to receive chemoradiotherapy or postoperative radiotherapy (standard fractionation)	250 ml solution of 400 mg recombinant Escherichia coli GM-CSF (Molgramostim) once daily as soon as erythema was diagnosed. Patients were instructed to swish and swallow over a period of 1 h	250 ml solution of the conventional mouthwash containing pantocain, hydrocortisone acid, cional kreussler and bepanthen	Trial was stopped early due to lack of effect of GM-CSF mouthwash. Mouthwash was started when WHO grade 1 oral mucositis was evident. No significant difference in the incidence of progression to more severe mucositis grades between groups. Pain scores were comparable across both groups.
Stokman MA, Spijkervet FKL, Burlage FR, Dijkstra PU, Manson WL, De Vries EGE, et al., 2003	RCT	Patients with a malignant tumour in the head and neck regions to be treated with primary curative or postoperative radiotherapy delivered in standard fractions	1 g containing polymyxin E 2 mg, tobramycin 1.8 mg and amphotericin B 10 mg (PTA) lozenges four times daily starting the first day of irradiation during the total radiation period	placebo lozegne	During the 5-week observation period, 89% of the patients in the PTA group developed pseudomembranes and in the placebo group 94%. The mucositis according to the WHO score stated as not differing throughout the study period between both groups,

					however no results presented.
Stokman MA, Spijkervet FKL, Burlage FR, Roodenburg JLN., 2005	case series (compared to historical controls)	Patients with a malignant tumor in the head and neck region to be treated with primary curative or postoperative radiotherapy delivered in standard fractions.	flurbiprofen (15 mg) tooth patch once a day before sleep at night to the same natural tooth or the upper denture to the buccal side. Patients administered the patches themselves starting 1 week before the start of radiotherapy, and on each following night. The medication was applied until completion of the course of radiotherapy.		The flubiprofen tooth patch was not effective at preventing mucositis or reducing severity in comparison to historical control data.
Su CK, Mehta V, Ravikumar L, Shah R, Pinto H, Halpern J, et al., 2004	RCT	patients with stage II-IVM0 carcinoma of the head and neck, who were scheduled to receive radiation delivered in standard fractions either as radical or postoperative therapy.	aloe vera solution consisting of 94.5% aloe juice, 5.0% pear juice concentrate, 0.4% lemon-lime flavor, and 0.1% citric acid, 20-mL swish and swallow four times daily, beginning on the first day and continuing throughout the RT course	taste matched placebo (aloe vera replaced by water, all other ingredients identical)	Aloe vera group had similar incidence of grade 2-3 mucositis compared to placebo group. No other data was presented for mucositis.
Su YB, Vickers AJ, Zelefsky MJ, Kraus DH, Shaha AR, Shah JP, et al., 2006	RCT (double-blind placebo-controlled)	Patients with squamous cell carcinoma of the head or neck region scheduled to receive post-operative radiotherapy in standard dose fractions	G-CSF administered at a dose of 3 ug/kg by daily subcutaneous (SC) injection, 7 days per week, starting 3 days before starting radiation, and continuing until the end of radiotherapy.	placebo injections	Study closed early due to slow accural of patients. Incidence and severity of mucositis appeared lower in the treatment arm, although did not reach statistical significance.
Trotti A, Garden A, Warde P, Symonds P, Langer C, Redman R, et al., 2004	RCT (double blind)	patients over 18 years old with pathologically confirmed diagnosis of cancer involving the oral cavity, oropharynx, nasopharynx, larynx, hypopharynx, or major salivary gland. In addition to	9 mg doses of iseganan, formulated as a 0.3% aqueous vehicle solution plus institute-specific standard-of-care (SOC) management of oral hygiene instructed to self-administer study drug six	placebo + SOC administered identically	The two groups were comparable in terms of incidence of any and severe mucositis, as well as peak severity and average severity of mucositis. The extra group (SOC only) was not blinded

		conventional RT, four different schedules of altered fractionation were allowed for unresected disease: hyperfractionation delivering 1.2 Gy per fraction twice a day to a total dose of 72.0?81.6 Gy,concomitant boost RT delivering 72 Gy over 6 weeks using twice-a-day treatment during the last 2.5 weeks, an accelerated regimen delivering 60 Gy in 25 fractions (2.4 Gy per fraction) over 5 weeks, and accelerated RT consisting of 1.6 Gy per fraction twice a day to a total dose of 64 Gy in 4 weeks. In addition, 3.5% of the patients received intensity-modulated RT. Conventional fractionation RT alone or conventional fractionation RT followed by hyperfractionated accelerated RT was used for patients receiving chemoradiotherapy. There was no restriction on the type or schedule of chemotherapy administered.	times daily throughout the RT administration period. Patients rinsed their mouths with water before administration of each dose of study drug. Study drug was swished in the mouth to cover all surface areas and gargled to ensure coverage of the oropharynx for 2 min and then swallowed.		and hence excluded form the current analysis, however authors found a significant difference between the iseganan group and the SOC only group in terms of OM incidence and severity. These results are potentially biased.
Vacha P, Fehlauer F, Mahlmann B, Marx M, Hinke A, Sommer K, et al., 2003	RCT	Patients with head and neck cancer scheduled to receive postoperative conventionally fractionated RT (5 2 Gy/week) the total dose was 60 Gy for completely resected tumors (R0) and 70 Gy in patients with incomplete resection (R1?2). 70 mg/m2 carboplatin was applied on treatment day 1-5 and 29-33 just before an	250 mg amifostine (Ethyol®)was given intravenously as short infusion over a period of 10-15 min. Then, within 15 min, a fraction of radiation was delivered.	nothing	authors state that mucosal toxicity of grade 3 (NCI CTC) occurred only in the control group. During the whole course of the therapy, mucosal reactions were less severe in the group treated with amifostine. The difference of the mean values was most pronounced in the 2nd week of treatment (p = 0.05) as shown

		RT session.			by a bar graph. However, no raw data or variance was presented in text making it hard to accept p value.
Veerasarn V, Phromratanapongse P, Suntornpong N, Lorvidhaya V, Sukthomya V, Chitapanarux I, et al., 2006	RCT	Patients with newly diagnosed stage T1-3 or post operativeT4, N 0-1, M0 squamous cell carcinoma of head and neck cancer (oral cavity, oropharynx, hypopharynx, and nasopharynx) and who had > 70% of both parotid glands within the radiation field scheduled to receive standard fraction radiotherapy	200 mg/m2 of Amifostine (Ethyol®) diluted in normal saline by means of 50 ml. intravenous infusion over a period of 3-5 minutes daily 30 minutes before each radiation treatment	nothing	The incidence of grade 2 or higher mucositis was less in the amifostine group from week 4 to the end of radiotherapy compared to control group. Unblinded study at risk of bias.
Veness MJ, Foroudi F, Gebski V, Timms I, Sathiyaseelan Y, Cakir B, et al., 2006	RCT (double-blind placebo-controlled)	patients with histologically confirmed mucosal squamous cell carcinoma (SCC) of the head and neck. Patients could receive radiotherapy in the adjuvant or definitive settings. Those receiving both chemotherapy and radiotherapy were also eligible.	Two hours before radiotherapy, the patients were advised to dissolve the misoprostol (200 mg) in 15 mL of water and then swish it around the oral cavity for 2 min, gargle and swallow.	identical placebo	Incidence of mucositis was similar between groups. Pain was worse in the misoprostol group.
Warde P, O'Sullivan B, Aslanidis J, Kroll B, Lockwood G, Waldron J, et al., 2002	RCT (double blind)	patients with squamous cell head-and-neck cancer scheduled to receive RT with inclusion of 50% of both parotid glands in the radiation fields to doses above 50 Gy as definitive or adjuvant treatment. A wide variety of dose fractionation schemes were used during this period. Most were treated with 60-70 Gy in 2-Gy daily fractions.	pilocarpine 5 mg tablets 3 times daily started on Day 1 of RT and continued until 1 month after completion of RT	identical placebo	No significant difference between groups in incidence of oral mucositis at any severity

		Other fractionation schemes included 60-64 Gy in 40 fractions during 4 weeks using twice-daily treatments, 50 Gy in 25 daily fractions, 60 Gy in 25 daily fractions, and 51 Gy in 20 daily fractions.			
Wijers OB, Levendag PC, Harms ER, Gan-Teng AM, Schmitz PI, Hendriks WD, et al., 2001	RCT	patients with a biopsy-proven malignant tumor of the head and neck, to be treated by either primary or postoperative external beam radiation therapy delivered by conventional fractionation schedules	adhesive mouth paste containing hypromellose (16%) in a mixture of white paraffine (57%) and paraffine (24%) was used as a vehiculum, the active PTA paste contained 0.2% Polymyxin E sulfate (Colistin sulfate), 0.18% Tobramycin and 1% Amphotericin B. Patients were instructed to apply 1 gram of paste 4 times a day starting 3 days before EBRT, and the application was continued until the end of EBRT.	identical paste	No differences between groups for incidence of mucositis or severe mucositis. van der Schueren scoring system used to grade mucositis.
Wu HG, Song SY, Kim YS, Oh YT, Lee CG, Keum KC, et al., 2009	RCT	patients receiving primary RT, primary chemoradiotherapy, or postoperative RT for head and neck cancer performed with conventional fractionation. Concurrent chemotherapy with cisplatin was allowed	The patients were instructed to spray either the 50 ug EGF over the entire oral mucosa and then swallow the residual, twice daily, from the first day through week 5 of RT	placebo spray	Response rate was defined as the ratio of patients who did not develop oral mucositis (ie, RTOG grade <2 by weeks 4 and 5 of RT, excluding patients whose grade 2 mucositis persisted at week 4 or 5). The RR of the placebo group was 37%, while the RR of the EGF group was 64%. There was no significant difference in the incidence of severe mucositis between the groups.
Wu MH, Yuan B, Liu QF,	RCT (non-blinded)	patients with head-neck	Qingre Liyan Decoction 200 ml	Dobell's solution. Gargle and	Statistics used for comparing

Wang Q., 2007		carcinoma scheduled to receive radiotherapy	daily during the entire course of radiation (unclear frequency and method, eg swish or gargle etc)	swallow 5 - 8 times daily during radiation course	mucositis incidence between groups is unclear, although authors state a significant difference. Decoction appears to reduce incidence of severe mucositis compared to Dobell's solution. However results may be biased due to investigators being aware of group allocation.
Wygoda A, Maciejewski B, Skladowski K, Hutnik M, Pilecki B, Golen M, et al., 2009	comparable cohort of 66 consecutive patients	patients with head and neck cancer receiving radiotherapy	conventional fractionation radiotherapy (1.8 - 2 Gy/fraction 5 x week, 45 days total)	accelerated fractionation radiotherapy (1.8 Gy/fraction 7 x week, 38 days total)	Confluent mucositis was more frequent in the accelerated fractionation group compared to conventional fractionation however no statistics were completed as far as evident in text.
You WC, Hsieh CC, Huang JT., 2009	RCT (non-blinded)	Patients with head and neck cancer receiving radiotherapy delivered as conventional fractionations, with or without cisplatin + 5FU concurrent chemotherapy	indigowood root (IR) 0.5 g powder (SunTen Pharmaceutical Co. Ltd., Taiwan) in 30 mL double distilled water; gargled for 3 minutes before swallowing	normal saline	Indigowood root significantly reduced the incidence of grade 3 mucositis compared to saline. However results are likely biased since neither patient nor assessor were blind to group allocation

Appendix 5 – Excluded studies

MAStARI

Abramoff, M., Lopes, N., Lopes, L., Dib, L., Guilherme, A., Caran, E., et al., Low-level laser therapy in the prevention and treatment of chemotherapy-induced oral mucositis in young patients

Reason for exclusion: Not head and neck cancer study

Alterio D, Jereczek-Fossa BA, Zuccotti GF, Leon ME, Sale EO, Pasetti M, et al, Tetracaine oral gel in patients treated with radiotherapy for head-and-neck cancer: Final results of a phase II study

Reason for exclusion: Not prevention

Amrein PC, Clark JR, Supko JG, Fabian RL, Wang CC, Colevas AD, et al, Phase I trial and pharmacokinetics of escalating doses of paclitaxel and concurrent hyperfractionated radiotherapy with or without amifostine in patients with advanced head and neck carcinoma

Reason for exclusion: RCTs available for i.v. amifostine

Arora H, Pai KM, Maiya A, Vidyasagar MS, Rajeev A., Efficacy of He-Ne Laser in the prevention and treatment of radiotherapy-induced oral mucositis in oral cancer patients.

Reason for exclusion: RCTs are available for this intervention, current study is a phase II non-randomised controlled trial

Bensadoun RJ, Daoud J, El Gueddari B, Bastit L, Gourmet R, Rosikon A, et al. , Comparison of the efficacy and safety of miconazole 50-mg mucoadhesive buccal tablets with miconazole 500-mg gel in the treatment of oropharyngeal candidiasis - A prospective, randomized, single-blind, multicenter, comparative, phase III trial in patients treated with radiotherapy for head and neck cancer.

Reason for exclusion: Not prevention

Bernier J, Thames HD, Smith CD, Horiot JC., Tumor response, mucosal reactions and late effects after conventional and hyperfractionated radiotherapy.

Reason for exclusion: Retrospective analysis of toxicity in RCT. Prospective study available

Birnbaum A, Dipetrillo T, Rathore R, Anderson E, Wanebo H, Puthwala Y, et al. , Cetuximab, paclitaxel, carboplatin, and radiation for head and neck cancer: A toxicity analysis.

Reason for exclusion: No comparisons

Buntzel J, Schuth J, Kuttner K, Glatzel M., Radiochemotherapy with amifostine cytoprotection for head and neck cancer.

Reason for exclusion: Data published in Buntzel 1998 Ann Oncol

Cella D, Pulliam J, Fuchs H, Miller C, Hurd D, Wingard JR, et al. , Evaluation of pain associated with oral mucositis during the acute period after administration of high-dose chemotherapy.

Reason for exclusion: Secondary analysis, and the proportion of patients with head and neck cancer in original study is unclear

Colella G, Cannavale R, Vicidomini A, Rinaldi G, Compilato D, Campisi G., Efficacy of a spray

compound containing a pool of collagen precursor synthetic aminoacids (l-proline, l-leucine, l-lysine and glycine) combined with sodium hyaluronate to manage chemo/radiotherapy-induced oral mucositis: preliminary data of an open trial.

Reason for exclusion: Treatment not prevention of mucositis

Dodd MJ, Dibble SL, Miaskowski C, MacPhail L, Greenspan D, Paul SM, et al., Randomized clinical trial of the effectiveness of 3 commonly used mouthwashes to treat chemotherapy-induced mucositis.

Reason for exclusion: treatment not prevention of mucositis

Dodd MJ, Miaskowski C, Dibble SL, Paul SM, MacPhail L, Greenspan D, et al. , Factors influencing oral mucositis in patients receiving chemotherapy.

Reason for exclusion: no intervention data for mucositis

Dodd MJ, Miaskowski C, Greenspan D, MacPhail L, Shih AS, Shiba G, et al. , Radiation-induced mucositis: A randomized clinical trial of micronized sucralfate versus salt & soda mouthwashes.

Reason for exclusion: treatment not prevention of mucositis

Duncan GG, Epstein JB, Tu DS, El Sayed S, Bezjak A, Ottaway J, et al., Quality of life, mucositis, and xerostomia from radiotherapy for head and neck cancers: A report from the NCICCTG HN2 randomized trial of an antimicrobial lozenge to prevent mucositis.

Reason for exclusion: Secondary analysis of a published article and contains no mucositis data

Geeta SN, Padmanabhan TK, Samuel J, Pavithran K, Iyer S, Kuriakose MA., Comparison of acute toxicities of two chemotherapy schedules for head and neck cancers.

Reason for exclusion: No description of method used to score mucositis, data collected retrospectively

Grotz KA, Wustenberg P, Kohnen R, Al-Nawas B, Henneicke-Von Zepelin HH, Bockisch A, et al., Prophylaxis of radiogenic sialadenitis and mucositis by coumarin/troxerutine in patients with head and neck cancer - A prospective, randomized, placebo-controlled, double-blind study.

Reason for exclusion: No mucositis data shown

Haddad R, Sonis S, Posner M, Wirth L, Costello R, Braschayko P, et al. , Randomized phase 2 study of concomitant chemoradiotherapy using weekly carboplatin/paclitaxel with or without daily subcutaneous amifostine in patients with locally advanced head and neck cancer.

Reason for exclusion: Study was closed early due to change in radiotherapy technique and slow accural

Haddad R, Wirth L, Costello R, Weeks L, Posner M., Phase II Randomized Study of Concomitant Chemoradiation Using Weekly Carboplatin/Paclitaxel with or without Daily Subcutaneous Amifostine in Patients with Newly Diagnosed Locally Advanced Squamous Cell Carcinoma of the Head and Neck.

Reason for exclusion: Review article

Hejna M, Kostler WJ, Raderer M, Steger GG, Brodowicz T, Scheithauer W, et al., Decrease of duration

and symptoms in chemotherapy-induced oral mucositis by topical GM-CSF: Results of a prospective randomised trial.

Reason for exclusion: Study of mucositis treatment not prevention

Hong JP, Lee SW, Song SY, Ahn SD, Shin SS, Choi EK, et al., Recombinant human epidermal growth factor treatment of radiation-induced severe oral mucositis in patients with head and neck malignancies

Reason for exclusion: Study of mucositis treatment not prevention

Jham BC, Chen H, Carvalho AL, Freire AR., A randomized phase III prospective trial of bethanechol to prevent mucositis, candidiasis, and taste loss in patients with head and neck cancer undergoing radiotherapy: a secondary analysis.

Reason for exclusion: Secondary analysis of existing data

Kaushal V, Verma K, Manocha S, Hooda HS, Das BP., Clinical evaluation of human placental extract (placentrex) in radiation-induced oral mucositis

Reason for exclusion: Study of mucositis treatment not prevention

Koc M, Aktas E. , Prophylactic treatment of mycotic mucositis in radiotherapy of patients with head and neck cancers.

Reason for exclusion: Mucositis was assessed in an unclear way. Mycotic infections confuse the reporting

Kostrica R, Rottenberg J, Kvech J, Betka J, Jablonicky P., Randomised, double-blind comparison of efficacy and tolerability of diclofenac mouthwash versus placebo in mucositis of oral cavity by radiotherapy

Reason for exclusion: Study of mucositis treatment not prevention

Koukourakis MI, Tsoutsou PG, Karpouzis A, Tsiarkatsi M, Karapantzos I, Daniilidis V, et al., Radiochemotherapy with cetuximab, cisplatin, and amifostine for locally advanced head and neck cancer: a feasibility study.

Reason for exclusion: Patients unable to tolerate amifostine were given off protocol agents

Kouvaris J, Kouloulias V, Kokakis J, Matsopoulos G, Balafouta M, Miliadou A, et al. , Cytoprotective effect of amifostine in radiation-induced acute mucositis - a retrospective analysis.

Reason for exclusion: Retrospective study, RCTs are available

Law A, Kennedy T, Pellitteri P, Wood C, Christie D, Yumen O., Efficacy and Safety of Subcutaneous Amifostine in Minimizing Radiation-Induced Toxicities in Patients Receiving Combined-Modality Treatment for Squamous Cell Carcinoma of the Head and Neck

Reason for exclusion: Non-randomised or controlled study, RCTs are available

Lee S, Wu H, Song S, Kim Y, Oh Y, Lee C, et al. , The therapeutic effect of recombinant human epidermal growth factor (rhEGF) on mucositis in patients with head and neck cancer undergoing radiotherapy with or without chemotherapy: A double-blind placebo-controlled prospective phase II

multi-institutional clinical trial.

Reason for exclusion: abstract only

Lin YS, Lin LC, Lin SW, Chang CP., Discrepancy of the effects of zinc supplementation on the prevention of radiotherapy-induced mucositis between patients with nasopharyngeal carcinoma and those with oral cancers: Subgroup analysis of a double-blind, randomized study

Reason for exclusion: subgroup analysis of patients from previous RCT

Maddocks-Jennings W, Wilkinson JM, Cavanagh HM, Shillington D. , Evaluating the effects of the essential oils Leptospermum scoparium (manuka) and Kunzea ericoides (kanuka) on radiotherapy induced mucositis: a randomized, placebo controlled feasibility study.

Reason for exclusion: patients allocated to groups based on ability to gargle.

Mantovani G, Massa E, Astara G, Murgia V, Gramignano G, Lusso MR, et al., Phase II clinical trial of local use of GM-CSF for prevention and treatment of chemotherapy- and concomitant chemoradiotherapy-induced severe oral mucositis in advanced head and neck cancer patients: An evaluation of effectiveness, safety and costs.

Reason for exclusion: lack of detail to assess if groups were comparable

Masucci G, Broman P, Kelly C, Lindahl S, Malmberg L, Reizenstein J, et al. , Therapeutic efficacy by recombinant human granulocyte/monocyte-colony stimulating factor on mucositis occurring in patients with oral and oropharynx tumors treated with curative radiotherapy: A multicenter open randomized phase III study.

Reason for exclusion: Treatment of mucositis, not prevention

Momo K, Shiratsuchi T, Taguchi H, Hashizaki K, Saito Y, Makimura M, et al., Preparation and clinical application of indomethacin gel for medical treatment of stomatitis.

Reason for exclusion: Non-English paper

Nicolatou O, Sotiropoulou-Lontou A, Skarlatos J, Kyprianou K, Kolitsi G, Dardoufas K. , A pilot study of the effect of granulocyte-macrophage colony-stimulating factor on oral mucositis in head and neck cancer patients during X-radiation therapy: a preliminary report.

Reason for exclusion: Case series, RCTs are available

Nicolatou-Galitis O, Dardoufas K, Markoulatos P, Sotiropoulou-Lontou A, Kyprianou K, Kolitsi G, et al., Oral pseudomembranous candidiasis, herpes simplex virus-1 infection, and oral mucositis in head and neck cancer patients receiving radiotherapy and granulocyte-macrophage colony-stimulating factor (GM-CSF) mouthwash.

Reason for exclusion: Treatment of mucositis not prevention

Nicolatou-Galitis O, Sotiropoulou-Lontou A, Velegraki A, Pissakas G, Kolitsi G, Kyprianou K, et al. , Oral candidiasis in head and neck cancer patients receiving radiotherapy with amifostine cytoprotection.

Reason for exclusion: non-randomised study. RCTs are available for amifostine

Nikoletti S, Hyde S, Shaw T, Myers H, Kristjanson LJ. , Comparison of plain ice and flavoured ice for preventing oral mucositis associated with the use of 5 fluorouracil.

Reason for exclusion: Unclear the tumour type of patients under study

Ozsahin M, Betz M, Matzinger O, Bron L, Luthi F, Pasche P, et al. , Feasibility and efficacy of subcutaneous amifostine therapy in patients with head and neck cancer treated with curative accelerated concomitant-boost radiation therapy.

Reason for exclusion: A single group study. RCTs are available for s.c. amifostine

Peters K, Mucke R, Hamann D, Ziegler PG, Fietkau R. , Supportive use of amifostine in patients with head and neck tumors undergoing radio-chemotherapy: Is it possible to limit the duration of the application of amifostine.

Reason for exclusion: Unclear if groups are comparable. RCTs are available

Rabinovitch R, Grant B, Berkey BA, Raben D, Ang KK, Fu KK, et al., Impact of nutrition support on treatment outcome in patients with locally advanced head and neck squamous cell cancer treated with definitive radiotherapy: A secondary analysis of RTOG trial 90-03.

Reason for exclusion: Secondary analysis

Schonekas KG, Wagner W, Prott FJ., Amifostine--a radioprotector in locally advanced head and neck tumors.

Reason for exclusion: Groups not comparable. RCTs available

Simoes A, Eduardo FP, Luiz AC, Campos L, Sa PH, Cristofaro M, et al., Laser phototherapy as topical prophylaxis against head and neck cancer radiotherapy-induced oral mucositis: comparison between low and high/low power lasers.

Reason for exclusion: No usable data included. Groups not comparable in terms of experiment start or mucositis. Oral mucositis at onset of experiment.

Smith RV, Goldman SY, Beitler JJ, Wadler SS. , Decreased short- and long-term swallowing problems with altered radiotherapy dosing used in an organ-sparing protocol for advanced pharyngeal carcinoma.

Reason for exclusion: No data on measurement of mucositis. Authors state that OM was similar between 74 Gy and 60 Gy group at end of therapy.

Suntharalingam M, Jaboin J, Taylor R, Wolf J, Banglore M, Van Echo D, et al., The evaluation of amifostine for mucosal protection in patients with advanced loco-regional squamous cell carcinomas of the head and neck (SCCHN) treated with concurrent weekly carboplatin, paclitaxel, and daily radiotherapy (RT).

Reason for exclusion: RCTs for i.v. amifostine are available

Tejedor M, Valerdi JJ, Arias F, Dominguez MA, Pruja E, Mendez L, et al., Hyperfractionated radiotherapy concomitant with cisplatin and granulocyte colony-stimulating factor (filgrastim) for laryngeal carcinoma.

Reason for exclusion: Non randomised study, RCTs are available for G-CSF

Thorstad WL, Haughey B, Chao KSC. , Pilot Study of Subcutaneous Amifostine in Patients Undergoing Postoperative Intensity Modulated Radiation Therapy for Head and Neck Cancer: Preliminary Data.

Reason for exclusion: interim report

Trog D, Bank P, Wendt TG, Koscielny S, Beleites E., Daily amifostine given concomitantly to chemoradiation in head and neck cancer - A pilot study.

Reason for exclusion: RCTs are available for s.c. amifostine

Uchiyama Y, Murakami S, Kakimoto N, Nakatani A, Furukawa S. , Effectiveness of Cepharanthin in decreasing interruptions during radiation therapy for oral cancer.

Reason for exclusion: Very poorly described study at high risk of bias

Wagner W, Alfrink M, Haus U, Matt J. , Treatment of irradiation-induced mucositis with growth factors (rhGM-CSF) in patients with head and neck cancer.

Reason for exclusion: treatment of mucositis not prevention

Wagner W, Prott FJ, Schonekas KG. , Amifostine: a radioprotector in locally advanced head and neck tumors.

Reason for exclusion: RCTs available for amifostine

Zanin T, Zanin F, Carvalhosa AA, Castro PH, Pacheco MT, Zanin IC, et al., Use of 660-nm diode laser in the prevention and treatment of human oral mucositis induced by radiotherapy and chemotherapy.

Reason for exclusion: non-randomised study where comparability of groups is uncertain. RCTs avaiable for this intervention