RADIOPROTECTORS

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THE GOAL OF RADIOTHERAPY

TO DELIVER A SUFFICIENT DOSE TO THE TUMOR

PROBABILITY OF CURE

RISK OF TOXICITY

TO INDUCE MINIMAL DAMAGE IN THE SURROUNDING NORMAL TISSUES
SENSITIZATION OF TUMORAL TISSUES INCREASE DOSE OF RADIATION

PROTECTION OF NORMAL TISSUES REDUCE DOSE OF RADIATION

Therapeutic ratio

Probability of local tumor control

Probability of complications (---)

0 5% 0 100%

Dose in cGy
WAYS TO IMPROVE THE PROTECTION OF NORMAL TISSUES

PHYSICAL PROTECTION
- CONFORMAL RADIOTHERAPY

TECHNOLOGICAL PROTECTION
- 3D CONFORMAL RADIOTHERAPY
- INTENSITY-MODULATED RADIOTHERAPY
- RADIOSURGERY
- 4D IMRT (time varying anatomy: GATED RADIOTHERAPY)

BIOLOGICAL PROTECTION
- HYPERFRACTIONATION
- ULTRAFRACTIONATION

CHEMICAL PROTECTION
- CHEMICAL RADIOPROTECTORS

OTHERS
STEM CELLS THERAPY
GENE THERAPY
LASER
CHEMICAL RADIOPROTECTORS
- “Les radioprotecteurs sont des substances qui, présentes pendant l’irradiation, diminuent les effets de cette irradiation. Ils ne peuvent donc avoir qu’une action préventive”.


- “Compounds to protect normal tissues without a comparable reduction in the cytotoxic effect on tumor cells”.


- “Radioprotectors are chemicals that reduce the biologic effects of radiation”.

E.J. Hall in “Radiobiology for the radiologist”. Lippincot Williams & Wilkins Fith edition 2.000.

- “Ability of certain substances to provide protection against the damaging effects of ionizing radiation”.

HISTORICAL SUMMARY


- 1.951  BACQ  “Protection contre le rayonnement X par la beta-mercaptoethylamine (cysteamine)”. Arch. Inter. Physiol 59:442-447.


- 1.979  SWEENEY  “A survey of compounds from the Antiradiation Drug Development Program of the U.S. Army Medical Research and Development Command”. Walter Reed Inst. Res.


RADIOPROTECTIVE AGENTS IN RADIATION THERAPY

THE IDEAL CHEMICAL RADIOPROTECTOR

- PRESERVATION OF THE ANTI-TUMOUR EFFICACY OF RADIATION.
- WIDE WINDOW OF PROTECTION AGAINST ALL TYPES OF TOXICITY.
- TREATMENT-RELATED TOXICITY REDUCTION → DOSE ESCALATION.
- WIDE TISSUES PROTECTION.
- LOW TOXICITY PROFILE.
- EASY AND COMFORTABLE ADMINISTRATION.
- REASONABLE COST-EFFECTIVENESS.
NORMAL TISSUE RADIATION TOXICITY.

Traditional concept (target cell theory).

The historical view is that radiation-induced normal tissue damage consists of distinct and separate phases - an acute and a late phase - each due to the depletion of different target cell populations.
### Radiation therapy

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<th>Months</th>
<th>1</th>
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#### ACUTE EFFECTS

- Hierarchical, rapidly renewing tissues.
  - Stem cells killing.
  - The time onset of early reactions correlates with the lifespan of differentiated functional cells.
  - Latency < 90 days.
  - No strong dependence on extent of damage, but greater damage may lead to slower healing of injury.
  - Transient clinical course (surviving stem cells will repopulate and restore integrity of tissues).

If low level of surviving stem cells or additional trauma.

#### GENUINE LATE EFFECTS

- Flexible, slowly renewing tissues.
  - Functional cells killing or vascular cells killing (vascular injury model)
  - Latency > 90 days.
  - Shorter latent period with greater damage.
  - Irreversible clinical course. Compensatory mechanisms may occur.

#### CONSEQUENTIAL LATE EFFECTS

Late effects which in their frequency or severity are influenced by the severity (grade and duration) of the acute changes in the same tissue.

#### TOXICITY SCORING

- **RTOG (1.984)**
- **CTC v 2.0 (1.998)**

- **CTCAE v3.0 (October 2.003)**

  Common Terminology Criteria for Adverse Events
NORMAL TISSUE RADIATION TOXICITY.

What has changed over the years?

- Structural/functional manifestations of toxicity have not changed.

- Sequence of events has not changed.

- Understanding of the underlying pathobiology has changed.
NORMAL TISSUE RADIATION TOXICITY.

Contemporary thinking.

Normal tissue response to radiation is an integrated response involving cell death, the production of reactive oxygen species, alterations in gene expression and the production of cytokines.

Immediately after irradiation, an intracellular conversation is initiated resulting from damage to DNA or to damage to membrane or cytoplasmatic organelles.

Intercellular communication via released messenger RNA activates receptor cells through signal transduction, which results in additional cytokine expression.

Furthermore, cell to matrix interactions alter the extracellular matrix component of the tissue.

Thus within hours, days and weeks, alterations in gene expression and the induction of cytokines occur, all of which contribute to the expression of damage in tissues.
Well-known phenomena characterized by the “target cell model”. The time between irradiation and manifestation of injury depends on target cell characteristics (radiation sensitivity, repair capacity, proliferation rate, etc) and tissue organization.

Reactive phenomena that occur in response to radiation-injury in other cells or tissues, i.e. parenchymal cell depletion secondary to vascular damage. Also include such phenomena as the “bystander effect” and tissue reactions to cell lethality such as the effects of vasoactive, procoagulant and inflammatory mediators, including cytokines, growth factors and chemokines.

Result from nonlethal effects on different intra- and extracellular molecules and changes in gene expression in irradiated cells leading, for example, to direct inactivation of anticoagulant molecules, activation of latent growth factors and activation of proteases. They include phenomena such as the inhibition of cellular replicative ability and accelerated senescence that lead to decreased tissue vitality.

Tissue injury

- Signs & symptoms
  - acute
  - subacute
  - late
Examples of Secondary Effects.

. Hypercoagulability
. Cytokine production
. ROS generation

. Leukocyte adhesion
. Leukocyte chemotaxis
. Cytokine production
. ROS generation

ORIGIN
DYSFUNCTION

OXIDATIVE IMBALANCE

. Hypercoagulability
. Cytokine production
. Leukocyte chemotaxis
Examples of Functional Effects.

. Activation of protein kinase C
. Activation of AP-1, NF$_{k}$B
. Thrombomodulin inactivation
. Increased phospholipase A2 activity
. Decreased NOS, PGI$_2$, transglutaminase
NORMAL TISSUE

Parenchymal cells
- Parenchymal atrophy

Endothelial cells
- Vascular sclerosis
- Functional effect: Promote coagulation

Connective cells
- Fibrosis
- Functional effect: Inflammation
- Indirect effect: Inflammation

Cytocidal effect
- Indirect effect: Devascularization

Parenchymal atrophy

Vascular sclerosis

Fibrosis
Damaged NORMAL TISSUE
i.e. diabetes

Additional injuries
i.e. chemotherapy, infection

Cytocidal effect
Parenchymal cells
Parenchymal atrophy

Cytocidal effect
Endothelial cells
Vascular sclerosis

Functional effect:
Promote coagulation

Functional effect:
Inflammation

Indirect effect:
Inflammation

Indirect effect:
I. devascularization

Connective cells
Fibrosis

Additional injuries
i.e. chemotherapy, infection
Cytocidal effect

Functional effects

Indirect (secondary) effects

Proinflammatory cytokines

MUCOSITIS

Cytocidal effect
TISSUE INJURY

Activation of monocytes/macrophages/platelets

Release of cytokines and growth factors

FIBROBLASTS

recruitment

proliferation

increased

decreased

synthesis

degradation

of ECM

of ECM

FIBROYSIS

autoimmunity

diabetes

trauma

irritant dust

hypertension

Chemicals/radiation

infection

Tissue injury

Indirect effect: Inflammation

Cellular injury

Functional effect: Inflammation

Stress protein gene activation

Trauma

Irritant dust

Hypertension

Chemicals/radiation

Diabetes

Infection

Autoimmunity

Functional and indirect effects:

Inflammation

Cellular injury
Radiation therapy

ACUTE EFFECTS

SUBACUTE EFFECTS

LATE EFFECTS

Cytocidal effects:
Hierarchical, rapidly renewing tissues.
Stem cells killing.

Indirect effects (vascular cells killing)
Functional effects

Cytocidal effects:
Flexible, slowly renewing tissues.
Functional cells killing.

CTCAE v3.0 (October 2003)
Common Terminology Criteria for Adverse Events
RADIOPROTECTIVE AGENTS: AGENTS THAT SHIELD NORMAL HEALTHY CELLS AND TISSUES FROM THE EFFECTS OF RADIATION. PROTECTION. PROPHYLAXIS AGAINST THE EFFECTS OF RADIATION.


Radiation therapy

PROPHYLAXIS
Radioprotectors
Must be present at the time of irradiation

Latency
Clinical evidence of injury

TREATMENT
Stimulating agents
Reversal agents

Toxicity antagonists
Agents that directly interfere with the mechanism of toxicity or modulate the normal tissue response to injury.
CHEMICAL RADIOPROTECTORS AGAINST ACUTE EFFECTS
CHEMICAL RADIOPROTECTORS AGAINST ACUTE EFFECTS

ACUTE MUCOSAL INJURY
1- The efficacy of sucralfate suspension in the prevention of oral mucositis due to radiation therapy.
CONCLUSION: Prophylactic oral rising with sucralfate did not prevent oral ulcerative mucositis. Sucralfate may reduce the experience of pain during radiation therapy.

2- A prospective pilot study on the effect of sucralfate mouth-swishing in reducing stomatitis during radiotherapy of the oral cavity.
CONCLUSION: The present study suggests that oral sucralfate suspension is a useful agent in preventing or relieving radiation induced oral mucositis. Randomized trials are needed.

3- Sucralfate in the prevention of radiation-induced oral mucositis.
CONCLUSION: Sucralfate mouth washing is beneficial in decreasing the intensity of radiation-induced mucositis and oral discomfort. It is cheap, easy to administer with no serious side effect and may be routinely used in patients receiving head and neck radiotherapy.
CONCLUSION: Although the trial produced no direct clinical evidence indicating that sucralfate mouth rinses prevent radiation-induced mucositis, the decrease in the salivary lactoferrin and albumin levels suggests that sucralfate has a slight protective effect on the oral mucosa. (The efficacy of sucralfate is partly based on the formation of a protective barrier on damaged and normal mucosa, but also on stimulation of prostaglandin release, bicarbonate and mucus excretion and mucosa cell renewal.

CONCLUSION: A trend (that was not statistically significant) of less severe radiation mucositis was noted for patients receiving sucralfate in addition to the combination of viscous lidocaine, diphenhydramine, and antacid for non-ulcerative radiation mucositis.

CONCLUSION: This trial produced no clinical evidence indicating that the oral intake of sucralfate reduces the acute radiation-induced side-effects.

4- Effects of sucralfate on mucositis during and following radiotherapy of malignancies in the head and neck region. A double blind placebo-controlled study. L. Franzen and Al. Acta Oncol. 34:219-223 (1.995).
CONCLUSION: The study demonstrate that the proportion of patients with severe mucosal reactions was significantly lower in the sucralfate group than in the placebo group.

CONCLUSION: Prophylactic treatment with sucralfate during high-dose head and neck RT did not decrease acute treatment side effects.
1- The effect of chlorhexidine and benzydamine mouthwashes on mucositis induced by therapeutic irradiation.
CONCLUSION: These results indicate that, although the individual patient acceptance of chlorhexidine is better than benzydamine, there is little difference between the two mouthwashes both in controlling pain and mucositis or in the oral carriage of the microorganisms studied.

2- Effect of chlorhexidine rinsing on the oropharyngeal ecology in patients with head and neck cancer who have irradiation mucositis.
CONCLUSION: Suppression of oral flora and a lowering of the severity of mucositis by means of desinfecting mouthrinses were not successful.

3- Effect of selective elimination of the oral flora on mucositis in irradiated head and neck cancer patients.
CONCLUSION: Mucositis was significantly reduced compared with the previous two groups. The effect of selective elimination of gram-negative bacilli from the oropharynx and the prevention of severe mucositis may be explained by the eradication of these bacteria and or neutralization of salivary endotoxin, released by gram-negative bacilli mediating the inflammatory processes.

4- Topical administration of antimicrobial agents to prevent irradiation mucositis of the oral cavity and oropharynx: A pilot study.
CONCLUSION:
CONCLUSION: No differences were observed in oral mucositis between the control and chlorhexidine groups of patients undergoing high-dose radiotherapy.

CONCLUSION: In contrast to the prestudy hypothesis that a chlorhexidine mouthwash might provide benefit for patients receiving radiotherapy to the oral mucosa, this study provides strong evidence suggesting that a chlorhexidine mouthwash is detrimental in this clinical situation.

CONCLUSION: The present study has demonstrate that the use of pastilles containing tobramycin, polymyxin and amphotericin produced a reduction in mucositis problems that should be of sufficient magnitude to increase materially patient tolerance to radical radiotherapy for head and neck cancer.

CONCLUSION: This prospective, controlled trial provides evidence to suggest that a nonabsorbable antibiotic lozenge can decrease patient-reported radiation-induced oral mucositis to a modest degree. Nonetheless, this evidence does not appear to be compelling enough to recommend this treatment as part of standard practice.

5- Povidone-iodine to prevent mucositis in patients during antineoplastic radiochemotherapy. R. Rahn and Al. *Dermatology* 195(S2):57-61 (1.997).
CONCLUSION: Rinsing with povidone-iodine reduce significantly the incidence, severity and duration of oral mucositis during antineoplastic radiochemotherapy.
6- Prophylaxis with povidone-iodine against induction of oral mucositis by radiochemotherapy.
CONCLUSION: The results obtained indicate that incidence, severity and duration of radiochemotherapy-induced mucositis can be significantly reduced by oral rinsing with povidone-iodine in addition to the standard prophylaxis scheme. It can be concluded that rinsing with povidone-iodine is an easy, cheap and safe prophylactic method and can be recommended as a supportive treatment during antineoplastic treatment of the head and neck region.

7- Mucositis reduction by selective elimination of oral flora in irradiated cancers of the head and neck: A placebo-controlled double blind randomized study.
CONCLUSION: Selective elimination of aerobic Gram-negative bacteria of the oral flora did not result in a reduction of radiation-induced mucositis and therefore does not support the hypothesis that these bacteria play a crucial role in the pathogenesis of mucositis.

8- Prophylaxis of radiation-associated mucositis in conventionally treated patients with head and neck cancer: A double blind, phase III, randomized, controlled trial evaluating the clinical efficacy of an antimicrobial lozenge using a validated mucositis scoring system.
CONCLUSION: This study was conducted on the basis of a pilot study that demonstrated the BCoG lozenge (Bacitracin, Clotrimazole, Gentamicin) to be tolerable and microbiologically efficacious. A validated mucositis scoring system was used. However, in this group of patients treated with conventional radiotherapy, the lozenge did not impact significantly on the severity of mucositis. Wether such a lozenge would be beneficial in treatment situations where rate of severe mucositis is higher (ie, in patients treated with unconventional fractionation or with concomitant chemotherapy) is unknown.

CONCLUSION: Iseganan oral solution was safe but did not reduce the risk for developing ulcerative oral mucositis. Intensified oral hygiene or the administration of the vehicle used to deliver study drug in this trial appears to have reduced the risk and severity of oral mucositis. Our results suggest that antimicrobial intervention may not meaningfully affect the pathogenesis of radiation-induced oral mucositis.
OROPHARYNGEAL MUCOSITIS  SILVER NITRATE  
NON-RANDOMIZED TRIALS

1- Acute mucositis in the stimulated oral mucosa of patients during radiotherapy for head and neck cancer. 
CONCLUSION: In 16 patients treated for squamous cell carcinoma of the oral cavity or oropharynx with an accelerated 
split course regimen, acute mucosal reactions were significantly less in the left buccal mucosa which had been repeatedly 
painted with 2% silver-nitrate solution for several days before radiotherapy than in the unpainted right buccal mucosa.

2- Effects of stimulated repopulation on oral mucositis during conventional-radiotherapy. 
CONCLUSION: In a radiotherapy trial with conventional postoperative treatment with 5 X 2 Gy./week to a total dose of 
60 Gy. in 6 weeks, the left buccal mucosa in 10 patients with squamous cell carcinomas of the head and neck was 
conditioned (3% silver nitrate, 3 times per day, 5 days before and the first 2 days of radiotherapy) while the contralateral 
mucosa, receiving an identical dose, served as individual control. Mucositis score according to the EORTC/RTOG or the 
Dische system showed that the time course and severity of the mucosal response was almost identical in both cheeks.
OROPHARYNGEAL MUCOSITIS  BENZYMADINE.
RANDOMIZED TRIALS

1- Prevention of oral mucositis in radiation therapy: a controlled study with benzydamine hydrochloride rinse.
CONCLUSION: Benzydamine hydrochloride rinse was shown to prevent oral mucositis in radiation therapy.

2- Benzydamine HCL for prophylaxis of radiation-induced oral mucositis.  Results from a multicenter, randomized, double-blind, placebo-controlled clinical trial.
CONCLUSION: Benzydamine oral rinse was effective, safe and well tolerated for prophylactic treatment of radiation-induced oral mucositis.

3- CONFIRMATORY TRIAL IN PROGRESS
OROPHARYNGEAL MUCOSITIS  GLUTAMINE
RANDOMIZED TRIALS

1- Acute mucositis in the stimulated oral mucosa of patients during radiotherapy for head and neck cancer. Oral glutamine to alleviate radiation-induced oral mucositis: a pilot randomized trial.

CONCLUSION: Oral glutamine may significantly reduce the duration and severity of objective oral mucositis during radiotherapy. It may shorten the duration of > grade 3 subjective mucositis.
OROPHARYNGEAL MUCOSITIS CORTICOSTEROIDS. RANDOMIZED TRIALS


CONCLUSION: A trend favouring shorter treatment interruptions in the prednisone arm was found, but not a reduction in the intensity or duration of mucositis.
1- Efficacy and safety of granulocyte macrophage-colony stimulating factor (GM-CSF) on the frequency and severity of radiation mucositis in patients with head and neck carcinoma.
CONCLUSION: GM-CSF subcutaneous administration concurrently with conventional fractionated radiotherapy was feasible without significant toxicity. The acute effects of radiotherapy namely mucositis, pain and functional impairment were nil to minimal. The results are suggestive of mucosal protection by GM-CSF during radiotherapy and warrants further study in randomized double blind trial.

2- Evaluation of the efficacy and safety of GM-CSF in the prophylaxis of mucositis in patients with head and neck cancer treated with RT.
CONCLUSION: GM-CSF administration was well tolerated for almost all patients. The radiation side effects that were statistically evaluated, were milder in group A (GM-CSF) than in group B (control group). During week 6 moderate pain was present in 41,7% of patients in the control group versus 5,9% (p=0,004), severe pain was present in 25% vs 0% (p=0,004), extensive erythema was present in 41,7% vs 6,2% (p=0,009). Similarly, 42,1% of patients in control group had food intake with the use of narcotics vs 0% in group A (p=0,008). A comparative study with a larger number of patients will establish the use of GM-CSF in the prophylaxis of radiation mucositis.

CONCLUSION: GM-CSF is an effective treatment for preventing mucositis produced by chemotherapeutic and/or radiotherapeutic interventions in patients at high risk of oropharyngeal mucosal damage.

4- Hyperfractionated radiation therapy and 5-fluorouracil, cisplatin, and mitomycin-C (+/- granulocyte-colony stimulating factor) in the treatment of patients with locally advanced head and neck carcinoma.
A.A. Abitbol and Al. Cancer 80(2):266-276  (1.997).
CONCLUSION: This regimen was feasible and effective but caused severe mucositis. No benefit was derived from the addition of G-CSF. This regimen deserves further modification to reduce acute mucositis toxicity yet maintain the high locoregional control rate.
CONCLUSION: The local administration of GM-CSF significantly reduced and almost healed radiation-induced oral mucositis in 14 of 17 patients during the radiotherapy, which was completed within the preplanned time and without any significant patient weight loss or functional impairment.

6- The effect of granulocyte colony-stimulating factor on oral mucositis in head and neck cancer patients treated with hyperfractionated radiotherapy.
M. Mascarin and Al.  Oral Oncol. 35:203-208 (1.999).
CONCLUSION: No statistically significant differences were found between the two groups except for the number of patients who interrupted the treatment: 69% in the RT group vs 23% in the RT+G-CSF group (p<0.005). Our observation indicate that G-CSF did not appear to have influenced the objective mucositis although it reduced the number of treatments breaks. In consideration of the cost of G-CSF, its prophylactic administration should be reserved only for patients at high risk of RT interruption.

7- Hyperfractionated radiotherapy concomitant with cisplatin and granulocyte colony-stimulating factor (filgastrim) for laryngeal carcinoma.
CONCLUSION: The administration of filgastrim with this regimen was feasible, and it appears to reduce the severity and duration of mucositis induced by the combined treatment.
OROPHARYNGEAL MUCOSITIS G-CSF/GM-CSF RANDOMIZED TRIALS

1- Filgastrim (r-metHuG-CSF) and its potential use in the reduction of radiation-induced oropharyngeal mucositis: an interim look at a randomized, double-blind, placebo-controlled trial.
CONCLUSION: No statistically significant between-group differences were seen in mean worst scores across time using repeated measures analysis of variance. At almost all timepoints, however, the worst mean scores were lower in patients treated with filgastrim compared with those in patients treated with placebo, and the number of severe mucositis scores was significantly lower in the filgastrim-treated group. Filgastrim may decrease the severity of radiation-induced oral/oropharyngeal mucositis.

2- Granulocyte macrophage-colony stimulating factor (GM-CSF) and sucralfate in prevention of radiation-induced mucositis: a prospective randomized study.
CONCLUSION: We found no evidence indicating that subcutaneous given GM-CSF reduces the severity of radiation-induced mucositis.

3- Analysis of the therapeutic efficacy induced by recombinant human GM-CSF on mucositis occurring in patients with oral-oropharynx tumors treated with curative radiotherapy. A multicenter open randomized phase III study.
G. Masucci and Al.  *Proceed. ESTRO meeting. Radiother. Oncol.* 64S1:166  (2.002)
CONCLUSION: Application of GM-CSF in RT induced mucositis is significantly more effective than traditional treatment and can be recommended as first line treatment in severe mucositis.

CONCLUSION: GM-CSF mouthwashes may be moderate more effective than sucralfate mouthwashes in preventing radiation-induced mucositis and mucositis-related pain, and their use may lead to less frequent RT course interruptions from mucositis. The present findings need to be confirmed before adopting GM-CSF mouthwashes in routine clinical use.
OROPHARYNGEAL MUCOSITIS KGF
NON-RANDOMIZED STUDIES

1- Amelioration of radiation-induced oral mucositis by keratinocyte growth factor: experimental studies.
CONCLUSION: These results indicate a marked increase in oral mucosal radiation tolerance by rhKGF which is most pronounced if the growth factor is applied one day prior to single dose irradiation, or during fractionated radiotherapy. The effect seems to be based on complex mechanisms, including changes in both epithelial proliferation and differentiation processes.

2- Phase II study of recombinant human keratinocyte growth factor (rHuKGF) in head and neck cancer treated with standard (SRT) or hyperfractionated irradiation (HRT) & concurrent chemotherapy (CT).
CONCLUSION: This trial suggests that rHuKGF reduces morbidity from HRT/CT but not from SRT/CT. SRT may require a different dose schedule than HRT.

3- Amelioration of acute oral mucositis by keratinocyte growth factor: fractionated irradiation.
CONCLUSION: In conclusion, these results indicate a marked increase in oral mucosa radiation tolerance by rHuKGF, which is most pronounced if the growth factor is applied during fractionated radiotherapy.
OROPHARYNGEAL MUCOSITIS  AMIFOSTINE
NON-RANDOMIZED TRIALS

1- Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer.
CONCLUSION: Amifostine was effective in reducing mucositis and dysphagia resulting from radiochemotherapy in patients with head and neck cancer. Furthermore, amifostine reduced the severity of late xerostomia. Amifostine treatment did not affect the clinical outcome.

2- Prophylactic use of amifostine to prevent radiochemotherapy-induced mucositis and xerostomia in head-and-neck cancer.
CONCLUSION: Amifostine was effective in reducing mucositis and dysphagia resulting from radiochemotherapy in patients with head and neck cancer. Furthermore, amifostine reduced the severity of late xerostomia. Amifostine treatment did not affect the clinical outcome.
OROPHARYNGEAL MUCOSITIS AMIFOSTINE
RANDOMIZED TRIALS


CONCLUSION: Despite the limited number of patients, this pilot randomized study suggests that amifostine was able to markedly reduce the severity and duration of mucositis induced by very accelerated radiotherapy. However, the tolerance of this twice daily amifostine schedule was relatively poor.


CONCLUSION: Amifostine reduced acute and chronic xerostomia. Antitumor treatment efficacy was preserved. No effect on acute mucositis.


CONCLUSION: ChRT by means of concomitant Paclitaxel and accelerated RT is feasible. Locoregional control is extremely promising, albeit at the cost of significant acute toxicity. Amifostine SC is more practical for use on a daily basis. So far, in this trial there is no evidence that Amifostine 500 mg SC reduces the severity of acute mucosal toxicity and/or preserves salivary flow substantially. One could argue that this is due to: 1) the significant toxicity of the applied ChRT scheme, 2) too low a dose of Amifostine for the SC route of administration, and 3) non-optimal treatment techniques used: IMRT was not implemented and with the 3DCRT techniques per se, an increase of the oral cavity mucosal dose was observed (and therewith a reduction of the minor salivary gland function).


CONCLUSION: According to our results, there is a radioprotective effect on salivary glands and a potential effect on oral mucosa by amifostine in postoperative radiotherapy combined with carboplatin. To improve the radio- and chemoprotective effects of amifostine in clinical practice, the application of a higher dose (> 250 mg) seems to be necessary.
OROPHARYNGEAL MUCOSITIS  PILOCARPINE
RANDOMIZED TRIALS


CONCLUSION: The significant difference in unstimulated salivary flow advocates for the concomitant use of oral pilocarpine to decrease radiation associated xerostomia. Oral pilocarpine did not influence the onset or grade of mucositis. Patients could not distinguish xersotomia from mucositis and their affect on QOL, thus, having the latter (mucositis) results in no improvement in QOL.
OROPHARYNGEAL MUCOSITIS PROSTAGLANDIN ANALOG
NON-RANDOMIZED TRIALS

1- Assessment of quality of life and oral function of patients participating in a phase II study of radioprotection of oral and pharyngeal mucosa by the prostaglandin E₁ analog misoprostol (RTOG 96-07).
   CONCLUSION: Although the sample size for this study was small, it appears that Misoprostol delivered swishing and swallowing did not protect the mucosa for this group of patients and may have contributed to increased toxicity.

2- Local prostaglandin E₂ in patients with oral malignancies undergoing chemo- and radiotherapy.
   CONCLUSION: Patients receiving PGE₂ reported substantially less intense pain than those in the control group. Our statistically results indicate that topical treatment of side effects produced by combined radio- and chemotherapy of oral neoplasms with PGE₂ holds promise and is clearly superior to conventional treatment modalities.
OROPHARYNGEAL MUCOSITIS  PROSTAGLANDIN ANALOG
RANDOMIZED TRIALS

1- Protection from radiation-induced oral mucositis by Misoprostol, a Prostaglandin E(1) Analog: A placebo-controlled, double-blind clinical trial.
CONCLUSION: The results of this pilot study suggest that misoprostol may protect the oral and pharyngeal mucosa from radiation-induced mucositis if adequate time between topical administration and radiation is allowed.
OROPHARYNGEAL MUCOSITIS  AZELASTINE
NON-RANDOMIZED TRIALS

1- Prophylaxis of oral mucositis associated with chemoradiotherapy for oral carcinoma by Azelastine hydrochloride (Azelastine) with other antioxidants.
CONCLUSION: A regimen including Azelastine, which suppresses reactive oxygen production and stabilizes cell membrane, may be useful for the prophylaxis of mucositis due to chemoradiotherapy.
1- Can prophylactic application of immunoglobulin decrease radiotherapy-induced oral mucositis?


CONCLUSION: The distribution of maximal mucositis degree revealed slightly more severe mucous membrane reaction in the control group compared with the immunoglobulin group (n.s.). The analysis of mean mucositis degrees in both groups demonstrated statistically significant differences (p=0.031) related to the entire group and to those 16 patients receiving radiation combined with chemotherapy. There was no significant immunoglobulin-induced effect on mucositis in patients treated by radiation alone. The time from the beginning of therapy to the first interruption could be prolonged 5 days in the immunoglobulin group (n.s.). In conclusion, it is demonstrated that the prophylactic application of immunoglobulin seems to lower the degree of radiation-induced mucositis.
OROPHARYNGEAL MUCOSITIS SOD
NON-RANDOMIZED TRIALS


CONCLUSION: Orgotein spray was well tolerated, easily applied, and no toxicity was observed. Orgotein oral spray substantially decreased the incidence and severity of mucositis in patients. 27% of the patients treated with orgotein versus 60% not receiving orgotein required interruption of treatment program. The difference was statistically significant (p=0.003). Orgotein oral spray exerts a protective action on the oral mucosa, it is well tolerated and shows no clinical signs of toxicity.
1- Management of oral mucositis during local radiation and systemic chemotherapy: a study of 98 patients.
CONCLUSION: Prophylactic oral care with Kamillosan Liquidum oral rinse appeared to modify oral environment favorably and maintain tissue integrity.
1- Phase II double-blind randomized study comparing oral Aloe Vera versus placebo to prevent radiation-related mucositis in patients with head-and-neck neoplasms.
CONCLUSION: In our randomized study, oral aloe vera was not a beneficial adjunct to head-and-neck radiotherapy. The mean quality-of-life scores were greater in the aloe vera group, but the differences were not statistically significant. Oral aloe vera did not improve tolerance to head-and-neck radiotherapy, decrease mucositis, reduce soreness, or otherwise improve patient well-being.
Prevention and treatment of chemotherapy- and radiotherapy-induced oral mucositis: a review

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Abstract

Oral mucositis is a distressing toxic effect of systemic chemotherapy with many commonly utilized drugs and of head and neck irradiation in patients with cancer. The agents and methods that have been used and studied in chemotherapy- and radiotherapy-induced oral mucositis, their mechanisms of action, and the current knowledge of their efficiency to reduce the incidence, severity or shorten the duration of oral mucositis are reviewed in this article. Oral cooling is a cheap and available method to lower the severity of bolus 5-fluorouracil-induced oral mucositis. However, more effective methods are needed. Results of studies with granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor are promising. Lasers are partly beneficial, but equipment-demanding. Modification of the chemotherapy regimen resulting in shortening of the exposition time to chemotherapy agents or chronomodulation of chemotherapy has been shown to lower mucosal toxicity of some regimens. Results of animal studies with locally applied transforming growth factor β3 and interleukin-11 are also promising. Based on the findings of the role of the inflammatory cascade in the response of normal tissues to chemotherapy and radiotherapy, anti-inflammatory drugs might be beneficial. At the present time, no agent has been shown to be uniformly efficacious and can be accepted as standard therapy of chemotherapy- and radiotherapy-induced oral mucositis. Further intensive research is needed. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Stomatitis prevention; Stomatitis control; Antineoplastic agents; Chemically induced; Radiotherapy-adverse effects
**LOCALLY APPLIED MEASURES AND PHARMACOTHERAPEUTICS**

A. Dental restoration

B. Oral hygiene

C. Mouth-coating agents: sucralfate, Kaolin-pectin.

D. Vitamins: Vitamin E, Tretinoin.

E. Antibiotics, Desinfectencia: Hydrogen peroxide, Chlorhexidin, Povidone-iodine solution, selective decontamination.

F. Anti-inflammatory agents: Chamomila, Betamethasone, Benzydamine, Mesalazine.

G. Cytokines: GM-CSF, TGF-beta3, EGF.

H. Eicosanoids: PGE1 (misoprostol), PGE2

I. Multiagent topical mouthrinses.

J. Epitelization promoting agents: Silver nitrate.

K. Antineoplastic agents antagonists: Leucovorin, Allopurinol.

**LOCALLY APPLIED NONPHARMACOLOGICAL METHODS**

A. Radiation shields.

B. Oral cooling (cryotherapy).

C. Soft laser.
SYSTEMICALLY APPLIED PHARMACOTHERAPEUTICS

A. Antioxidants: Beta-carotene, Azelastine.
B. Immunomodulatory drugs: Pentoxifylline, Indomethacin.
C. Anticholinergic drugs: Propantheline, Atropine.
D. Cytokines: G-CSF, GM-CSF, Interleukin 11.
E. Antiviral drugs: Acyclovir.
F. Metabolic substrate supplementation: Glutamine.
G. Hormone: Melatonin.
H. Other methods: Modification of the chemotherapy regimen, Chronotherapy.
PROPHYLAXIS OF ORAL MUCOSITIS IN IRRADIATED HEAD-AND-NECK CANCER PATIENTS: A PROPOSED CLASSIFICATION SCHEME OF INTERVENTIONS AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Purpose: To identify, classify, and evaluate agents used in the prophylaxis of oral mucositis in irradiated head and neck cancer patients.

Methods: Data sources included multiple databases and manual citation review of relevant literature. Based on the eligibility criteria, 59 studies were independently reviewed by two reviewers. Forty-two studies were included in the classification scheme, of which 15 met the criteria for inclusion in the meta-analysis. Data were extracted by duplicate independent review, with disagreement resolved by consensus.

Results: Overall, the interventions reduced the odds of developing severe oral mucositis, when assessed by clinicians, by 36% (OR: 0.64; 95% CI: 0.46, 0.88). Subgroup analysis suggested that only the narrow-spectrum antibacterial lozenges were effective (OR: 0.45; 95% CI: 0.23, 0.86); however, the power of the aggregated data in the other classes may have been insufficient to detect differences. When the outcome was assessed by patients, no significant difference was seen in the outcome between the treatment and the control groups (OR: 0.79; 95% CI: 0.56–1.12).

Conclusions: Overall, interventions chosen on a sound biologic basis to prevent severe oral mucositis are effective. In particular, when oral mucositis is assessed by clinicians, narrow-spectrum antibiotic lozenges appear to be beneficial. Methodologic limitations were evident in many of the studies. Further research using validated measurement tools in larger, methodologically sound trials is warranted. © 2001 Elsevier Science Inc.

Head and neck neoplasms, Radiotherapy, Drug therapy, Stomatitis, Clinical trials.
DIRECT CYTOPROTECTANTS

1. BARRIER FORMATION: sucralfate
2. STIMULATION OF EPITHELIAL RESPONSE
   2.1. PROSTAGLANDINS: PGE2, PGE1
   2.2. ANTIOXIDANTS: beta-carotene
   2.3. ASTRINGENTS: silver nitrate, hydrogen peroxide
   2.4. THIOLS: amifostine
   2.5. AMINO ACIDS: glutamine
   2.6. NON-PHARMACOLOGIC: low-energy laser

INDIRECT CYTOPROTECTANTS

1. HEMATOPOIETIC GROWTH FACTORS: G-CSF, GM-CSF
2. ANTI-INFLAMMATORY: indomethacin, benzydamine
3. IMMUNOGLOBULINS: human immunoglobulin

ANTIMICROBIALS

1. BROAD-SPECTRUM: chlorhexidine, povidone-iodine
2. NARROW-SPECTRUM: antibiotic/antifungal combinations
**Review: Mucositis**
**Comparison: Clinician Assessed Oral Mucositis**
**Outcome: Severe Mucositis (all trials)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>OR (95%CI Random)</th>
<th>Weight (%)</th>
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<td>8 / 15</td>
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<td>0.77 [0.18,3.21]</td>
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<td>22 / 52</td>
<td>25 / 50</td>
<td>17.0</td>
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<td>Total (95%CI)</td>
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<td>201 / 470</td>
<td>100.0</td>
<td>0.64 [0.46,0.88]</td>
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</table>

Chi-square 10.59 (df=11)

Fig. 1. Results of the meta-analysis for the outcome of clinician-assessed severe oral mucositis.
Review: Mucositis
Comparison: Patient-assessed Oral Mucositis
Outcome: Severe Mucositis (all trials)

<table>
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<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>OR (95%CI Random)</th>
<th>Weight %</th>
<th>OR (95%CI Random)</th>
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<td>0.77 [0.18,3.21]</td>
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<td>22 / 52</td>
<td>25 / 50</td>
<td>19.7</td>
<td>19.7</td>
<td>0.73 [0.34,1.60]</td>
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<td>Epstein, 1989</td>
<td>1 / 25</td>
<td>4 / 25</td>
<td>2.3</td>
<td>2.3</td>
<td>0.22 [0.02,2.11]</td>
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<tr>
<td>Feber, 1996</td>
<td>11 / 20</td>
<td>10 / 20</td>
<td>7.8</td>
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<td>1.22 [0.35,4.24]</td>
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<tr>
<td>Foote, 1994</td>
<td>24 / 25</td>
<td>20 / 27</td>
<td>2.5</td>
<td>2.5</td>
<td>8.40 [0.95,74.14]</td>
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<tr>
<td>Lievens, 1998</td>
<td>22 / 51</td>
<td>25 / 51</td>
<td>19.7</td>
<td>19.7</td>
<td>0.79 [0.36,1.72]</td>
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<td>Okuno, 1997</td>
<td>39 / 54</td>
<td>47 / 58</td>
<td>15.3</td>
<td>15.3</td>
<td>0.61 [0.25,1.48]</td>
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<td>Symonds, 1996</td>
<td>10 / 136</td>
<td>13 / 139</td>
<td>16.2</td>
<td>16.2</td>
<td>0.77 [0.33,1.82]</td>
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Total (95%CI) 147 / 412 163 / 412
Chi-square 7.38 (df=9) Z=1.34

Fig. 2. Results of the meta-analysis for the outcome of patient-assessed severe oral mucositis.
Clinical Practice Guidelines for the Prevention and Treatment of Cancer Therapy–Induced Oral and Gastrointestinal Mucositis

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Dorothy Keefe, M.D.⁴
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¹ Department of Palliative Care and Rehabilitation Medicine, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

BACKGROUND. Oral and gastrointestinal (GI) mucositis can affect up to 100% of patients undergoing high-dose chemotherapy and hematopoietic stem cell transplantation, 80% of patients with malignancies of the head and neck receiving radiotherapy, and a wide range of patients receiving chemotherapy. Alimentary tract mucositis increases mortality and morbidity and contributes to rising health care costs. Consequently, the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology assembled an expert panel to evaluate the literature and to create evidence-based guidelines for preventing, evaluating, and treating mucositis.

METHODS. Thirty-six panelists reviewed literature published between January 1966 and May 2002. An initial meeting in January 2002 produced a preliminary draft of guidelines that was reviewed at a second meeting the same year. Thereafter, a writing committee produced a report on mucositis pathogenesis, epidemiology, and scoring [also included in this issue], as well as clinical practice guidelines.

RESULTS. Panelists created recommendations from higher levels of evidence and suggestions when evidence was of a lower level and there was a consensus regard-
1- Prevention of irradiation-induced bowel discomfort by sucralfate.
CONCLUSION: radiation-induced bowel discomfort was reduced by the use of sucralfate.

2- Effects of sucralfate on acute and late bowel discomfort following radiotherapy of pelvic cancer.
CONCLUSION: It is suggested that sucralfate can be of beneficial value in diminishing bowel discomfort during treatment and, most importantly, sucralfate also reduces the late bowel disturbances that follow radiotherapeutic treatment of pelvic malignancies.

3- Does sucralfate reduce radiation-induced diarrhea?
CONCLUSION: Sucralfate *seems to be of importance in preventing radiation-induced diarrhea*. However, before any final conclusion can be drawn a randomized double blind trial using placebo is needed.
ACUTE ENTERITIS  SUCRALFATE  
RANDOMIZED TRIALS

1- Efficacy of sucralfate in the prophylaxis of diathea secondary to acute radiation-induced enteritis. Preliminary results of a double-blind randomized trial.
CONCLUSION: Sucralfate increases the enteric tolerance during pelvic irradiation in cancer patients.

2- Sucralfate in the prevention of treatment-induced diarrhea in patients receiving pelvic radiation therapy: a North Central Cancer Treatment Group phase III double-blind placebo-controlled trial.
CONCLUSION: Sucralfate did not decrease pelvic RT-related bowel toxicity by any of the end points measured and seems to have aggravated some gastrointestinal symptoms.

3- Does sucralfate reduce early side effects of pelvic radiation? A double-blind randomized trial.
CONCLUSION: Based on these results, the use of sucralfate can not be recommended as standard practice.
ACUTE ENTERITIS  SULPHASALAZINE  RANDOMIZED TRIALS

1- Double-blinded, randomized, placebo-controlled study to evaluate the effectiveness of sulphasalazine in preventing acute gastrointestinal complications due to radiotherapy.  
CONCLUSION: Sulphasalazine (2g/day) was found to be effective in decreasing the symptoms of acute radiation enteritis.
ACUTE ENTERITIS  5-ASA, MESALAZINE, OLSALAZINE.
RANDOMIZED TRIALS

1- A randomized trial to assess the efficacy of 5-aminosalicylic acid for the prevention of radiation enteritis.
CONCLUSION: 5-ASA has no protective effect against acute radiation enteritis and appears to worsen it.

2- A randomized double blind placebo controlled multicenter study of mesalazine for the prevention of acute radiation enteritis.
CONCLUSION: Mesalazine 4g/day did not decrease the symptoms of acute radiation enteritis.

3- Olsalazine is contraindicated during pelvic radiation therapy: results of a double-blind, randomized clinical trial.
CONCLUSION: Administration of Olsalazine during pelvic radiation therapy resulted in an increased incidence and severity of diarrhea. Olsalazine is contraindicated in patients receiving pelvic radiation therapy.

4- Randomized double-blind placebo-controlled trial of Balsalazide in the prevention of acute radiation enteritis as a consequence of pelvic radiotherapy.
CONCLUSION: Balsalazide is a new-generation 5-ASA drug with significant potential to prevent or reduce symptoms of acute radiation enteritis in patients undergoing pelvic radiotherapy. We feel that our pilot study justifies the formation of a cooperative group trial to assess its efficacy in a multi-institutional setting.
ACUTE ENTERITIS  MISC.
NON-RANDOMIZED TRIALS

1- Protection of the small intestine clonogenic stem cells from radiation-induced damage by pretreatment with interleukine-11 also increases murine survival time.
C.S. Potten and Al.  *Stem Cells* 14:452-459 (1.996).

2- Pretreatment with transforming growth factor beta-3 protects small intestinal stem cells against radiation damage in vivo.
CONCLUSION: The administration of TGF-beta 3 over a 24-hours period before irradiation increased the number of surviving crypts by four-to-six-fold after 14.5 Gy. Of radiation, only 35% of the animals survived within a period of about 12 days, while prior treatment with TGF-beta 3 provided significant protection against this early gastrointestinal animal death with 95% of the treated animals surviving for greater than 30 days.

3- Stimulation and inhibition of proliferation in the small intestinal crypts of the mouse after in vivo administration of growth factors.

4- Prophylactic glutamine protects the intestinal mucosa from radiation injury.
CONCLUSION: Glutamine exerts a protective effect on the small bowel mucosa by supporting crypt cell proliferation which may accelerate healing of the acutely radiated bowel.
ACUTE ESOPHAGITIS  SUCRALFATE
NON-RANDOMIZED TRIALS

1- The effect of sucralfate on the reduction of radiation induced esophagitis: clinical and laboratory data.
CONCLUSION: This data confirmed that sucralfate significantly reduce severe esophagitis symptoms during the radiation therapy course and made it easier for patients to tolerate the thoracic radiation treatment.
ACUTE ESOPHAGITIS  SUCRALFATE 
RANDOMIZED TRIALS

1- Phase III evaluation of sucralfate for radiation-induced esophagitis.
CONCLUSION: The results of this study failed to support our pre-study hypothesis. The sucralfate *did not alleviate esophagitis* but was related substantial gastrointestinal upset. Thus, this sucralfate solution should not be recommended for prevention or treatment of radiation-induced esophagitis.

- Placebo controlled trial of sucralfate for inhibiting radiation-induced esophagitis.
CONCLUSION: This oral sucralfate solution *does not appear to inhibit radiation-induced esophagitis* and is associated with disagreeable gastrointestinal side effects in this patient population.
ACUTE ESOPHAGITIS AMIFOSTINE RANDOMIZED TRIALS

1- Randomized phase III study of amifostine in patients treated with chemoradiation for inoperable stage II-III non-small cell lung cancer (NSCLC).
CONCLUSION: Amifostine significantly reduce acute pneumonitis and severe acute esophagitis although it caused significantly more hypotensive episodes.

2- Randomized phase III trial of radiation treatment +/- amifostine in patients with advanced-stage lung cancer.
CONCLUSION: Amifostine reduced the severity and incidence of acute esophageal, pulmonary, and hematologic toxicity resulting from concurrent cisplatin-based chemotherapy and RT. Amifostine had no apparent effect on survival in these patients with unresectable non-small-cell lung cancer, suggesting that it does not have a tumor-protective effect.

3- Randomized double-blind trial of combined modality treatment with or without amifostine in unresectable stage III non-small cell lung cancer.
CONCLUSION: Pretreatment with Amifostine showed a trend toward reducing the severity of esophagitis associated with concurrent chemoradiotherapy, but it did not reach statistical significance. There was no significant protective effect on hematologic or neurologic toxicities induced by paclitaxel and carboplatin.

4- Effect of amifostine on toxicities associated with radiochemotherapy in patients with locally advanced non-small cell lung cancer.
CONCLUSION: Amifostine is effective in reducing the incidence of both acute and late toxicities associated with radiochemotherapy in patients with locally advanced NSCLC without compromising antitumor efficacy. The incidence of grade ≥ 3 esophagitis durtine RCT was significantly lower for patients treated with RCT and amifostine than for patients treated with RCT alone (38,9% vs 84,4%; p<0.001).

CONCLUSION: Amifostine did not decrease the incidence or severity of esophagitis AUC in the schedule and dose given. However, patient-based evaluation demonstrated a reduction in swallowing difficulty based on esophagitis AUC, but not maximum grade. Pneumonitis was not improved in the amifostine arm. There was no evidence of compromised overall survival in patients receiving amifostine.
1- The effect of oral sucralfate on the acute proctitis associated with prostate radiotherapy: a double-blind, randomized trial.
CONCLUSION: This study suggests that oral sucralfate taken prophylactically during radiotherapy does not ameliorate the symptoms of acute radiation proctitis and may increase acute bleeding. The cause of the increased bleeding in the sucralfate group is unclear. As the pathogenesis of acute and late reactions are different, late follow-up, which includes sigmoidoscopic evaluation, is currently being performed on this cohort of patients.
ACUTE PROCTITIS  AMIFOSTINE
RANDOMIZED TRIALS

1- Protective effect of amifostine during fractionated radiotherapy in patients with pelvic carcinomas: results of a randomized trial.
CONCLUSION: The results of this randomized trial support the role of amifostine in reducing acute radiation-related toxicity of the bladder and lower gastrointestinal tract in patients with pelvic malignancies, without evidence of tumor protection.
1- Topical application of WR-2721 to prevent radiation-induced proctosigmoiditis.
CONCLUSION: This study showed that WR-2721 could be administered safely in enema form in doses ranging from 100 to 450 mg/enema, but this drug did not protect the rectosigmoid mucosa from radiation damage at the doses administered.

2- A pilot study of topical intrarectal application of amifostine for prevention of late radiation rectal injury.
CONCLUSION: Intrarrectal application of amifostine is feasible and well tolerated. Systemic absorption of amifostine and its metabolites is negligible, and close monitoring of patients is not required with rectal administration. Proctoscopy is superior to symptom score as a method of assessing radiation damage of the rectal wall. The preliminary efficacy data are encouraging, and further clinical studies are warranted.
1- Radiation-induced proctosigmoiditis: prospective, randomized double-blind controlled trial of oral sulfasalazine plus rectal steroids versus rectal sucralfate.
CONCLUSION: Both treatment regimens are effective in the management of radiation proctitis. Sucralfate enemas give a better clinical response, are tolerated better and because of the lower cost should be the preferred mode of short-term treatment.

2- A phase III double-blind randomised study of rectal sucralfate suspension in the prevention of acute radiation proctitis.
CONCLUSION: This study suggest that sucralfate given as a once daily enema does not substantially reduce the incidence of symptoms associated with acute radiation proctitis and its routine clinical use cannot be recommended. This cohort of patients will be followed to determine if any difference develops in relation to late toxicity.

3- A prospective randomized placebo-controlled double-blinded pilot study of misoprostol rectal suppositories in the prevention of acute and chronic radiation proctitis symptoms in prostate cancer patients.
CONCLUSION: Misoprostol rectal suppositories significantly reduce acute and chronic radiation proctitis symptoms in patients receiving radiation therapy for prostate cancer.