

RADIATION THERAPY ONCOLOGY GROUP

RTOG 96-07

A PHASE II STUDY OF RADIOPROTECTION OF ORAL AND PHARYNGEAL MUCOSA BY THE PROSTAGLANDIN E₁ ANALOG MISOPROSTOL

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SCHEMA

R

E

G Option 1: Post Op XRT and Misoprostol
(120 ± 15 mins before irradiation)

I

S Option 2: XRT only and Misoprostol
(120 ± 15 mins before irradiation)

T

E

R

Topical Oral and Pharyngeal Rinse:

Patient will swish and gargle misoprostol solution for 3-5 minutes and then swallow 120 minutes (± 15 minute variation in interval allowed) prior to irradiation. After the first day of treatment, misoprostol may be self-administered provided the patient is instructed on 1) how to dissolve one tablet in 15 cc of water, 2) how to swish, gargle, and swallow, and 3) how to complete a protocol worksheet. See Section 7.1.

Eligibility: (See Section 3.0 for details)

- Intact cancer of the oral cavity, oropharynx, supraglottic larynx, hypopharynx or nasopharynx, T₁-T₂, N₀-N₁.
- Completely resected margin-negative cancers of the oral cavity, oropharynx, supraglottic larynx or hypopharynx T₁-T₃, N₀-N₁.
- Planned irradiation of the oral cavity, pharynx or both at 2 Gy per day to total doses of 60 to 70 Gy over 6 to 7 weeks.
- No previous head and neck cancer or other malignancy (*except skin cancer*) except locally excised T1 N0 cancer NED after two years.
- No previous head and neck irradiation.
- No previous or concurrent chemotherapy.
- Women of child bearing age must not be pregnant and must use efficient contraception during treatment.
- KPS \geq 60, age \geq 18.
- Patients may not be registered on another treatment study using RT or chemotherapy.
- Signed study-specific informed consent.

Required Sample Size: 32

Institution # _____
RTOG 96-07
Case # _____

ELIGIBILITY CHECK (1/21/98)
(page 1 of 2)

- _____(Y/N) 1. Does the patient have an intact cancer of the oral cavity, oropharynx, hypopharynx, supraglottic larynx or nasopharynx clinically staged T1-2, N0-N1? *(If yes, skip to Q5)*
- _____(Y) 2. Is this patient with a completely resected cancer of the oral cavity, oropharynx, supraglottic larynx or hypopharynx staged T1-T3, N0-N1?
- _____(Y) 3. Based on light microscopy, are all resection margins negative with clearance of ≥ 5 mm?
- _____(Y) 4. Will radiation begin within 6 weeks of surgery?
- _____(≥ 18) 5. Age of patient.
- _____(≥ 60) 6. Karnofsky Performance Status.
- _____(N) 7. Has the patient received prior irradiation to the head or neck?
- _____(Y) 8. Is the patient able to gargle, swish and swallow the study agent *(per Section 7.0)*?
- _____(N) 9. Has the patient received any prior chemotherapy or is any planned during this course of treatment?
- _____(Y) 10. Have the patient and investigator agreed not to use chlorhexidine sucralfate or benzyhdramine hydrochloride during irradiation?
- _____(N) 11. Except for locally excised T1N0 cancer NED after 2 years or skin cancer, has the patient had another prior malignancy?
- _____(N) 12. Is the patient registered to another clinical protocol that uses chemotherapy or radiotherapy or is the patient eligible for RTOG 95-01?
- _____(N) 13. Does the patient have a known hypersensitivity to misoprostol (*Cytotec*) or other prostaglandins?
- _____(Y/N) 14. Does this patient have reproductive potential? *(If no, skip to Q17)*
- _____(Y/NA) 15. If female, was a pregnancy test performed with negative results within two weeks prior to study enrollment?

Institution # _____

RTOG 96-07

Case # _____

ELIGIBILITY CHECK (1/21/98)

(page 2 of 2)

_____(Y) 16. Has the patient agreed to use efficient contraception during treatment?

_____(Y) 17. Has the patient signed a study-specific consent form?

_____(Y/N) 18. Has the tumor been resected?

The following questions will be asked at Study Registration:

_____(Y) 1. Has the Eligibility Checklist (*above*) been completed?

_____(Y) 2. Is the patient eligible for this study?

_____ 3. Date the study-specific Consent Form was signed? (*must be prior to study entry*)

_____ Patient's Name

_____ Verifying Physician

_____ Patient ID #

_____ Referring Institution # (*if different*)

_____ Resection Prior to RT? (*yes vs. no*)

_____ Birthdate

_____ Sex

_____ Race

_____ Social Security Number

_____ Zip Code (*9 digit if available*)

_____ Method of Payment

_____ Will any component of the patient's care be given at a military or VA facility?

_____ Treatment Start Date

_____ Treatment Assignment

Completed by _____

Date _____

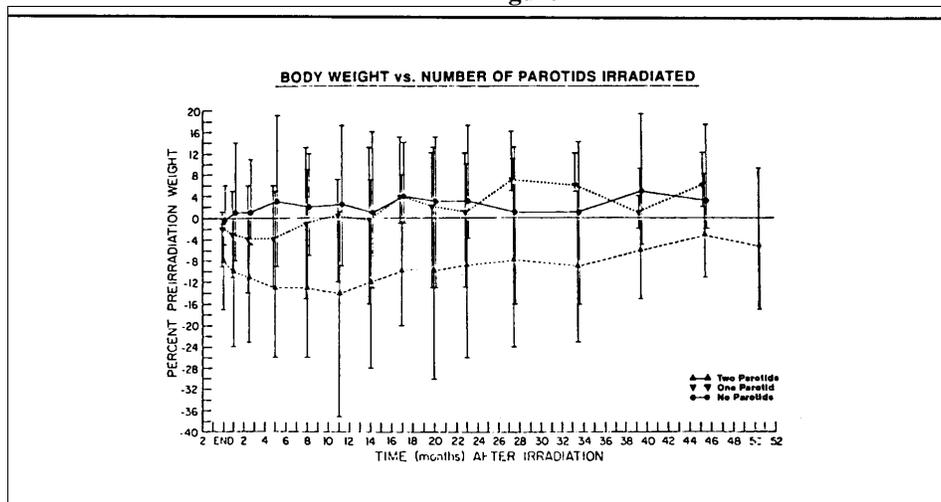
1.0 INTRODUCTION:

1.1 Background

Ionizing radiation is one of the most important modalities for the treatment of intact head and neck cancer with curative intent and is commonly employed to eradicate microscopic residual disease after surgery. The acute and late effects of radiation on normal tissues limit the total dose that can be delivered safely. If it were possible to protect the oral and pharyngeal mucous membranes from the acute effects of irradiation, patient morbidity would be substantially reduced and it would be possible to use chemotherapeutic agents that also cause an acute desquamation of mucosal epithelium. Increase in total radiation dose and size of daily fractions might still be limited by the late effects of ionizing radiation on the vasculoconnective tissue of bone and cartilage in the head and neck region. Nonetheless, radioprotection of mucous membranes would reduce morbidity and make possible the concurrent use of cytotoxic drugs.

During a course of fractionated external irradiation for head and neck cancer the rapidly dividing mucosal epithelium is progressively depleted with each succeeding radiation fraction. An acute radio-epithelialitis begins during the third week of fractionated external irradiation, gradually increases in intensity until the end of irradiation, and then subsides over several weeks thereafter. Erythema characterizes the early mucosal reaction, erythema and patchy ulceration the intermediate, and erythema and confluent ulceration, the end. The severity of radiation-induced mucositis varies for individual patients and ranges from mild to severe with most experiencing a moderate degree of mucosal desquamation by the end of a conventional fractionated course of irradiation. The acute mucosal reaction makes it difficult for patients to eat and swallow and impairs their ability to ingest food and fluids. Chencharick and Mosman noted that caloric intake was reduced to 70% of the recommended daily allowance of 2400 cal for patients undergoing irradiation for head and neck cancer.¹ The amount of weight loss depends on the severity of the radiation reaction, volume irradiated, size of individual fractions, total radiation dose, and salivary function. Donaldson studied 122 patients irradiated for head and neck cancer and reported greater absolute loss in body weight with increasing dose. Fourteen (8.7%) of 122 patients lost more than ten percent of their body weight during the course of irradiation.² Marks found that body weight was unaffected in a group of patients irradiated with small fields for cancers of the true vocal cord, that it declined to 4% below normal and returned to baseline within the year after parotid-sparing irradiation for cancers of the parotid and skin and that it declined 10 to 14% below normal for patients irradiated with large fields for cancers of the tonsil and nasopharynx (*Fig. 1*).³ The latter patients experienced a relatively slow rise in body weight over the ensuing four years predominantly due to the permanent loss of saliva and to a lesser degree the impairment in mastication and deglutition that results from operation and irradiation.

Figure 1



A fundamental problem in the combined use of drugs and ionizing radiation in the treatment of head and neck cancer is the overlapping toxicity of both modalities. In particular, the acute desquamation and ulceration of mucosal epithelium that results from fractionated irradiation and chemotherapy is more

severe when both are given simultaneously. The concurrent administration of cytotoxic drugs with irradiation often causes such a severe mucosal reaction that radiation has to be interrupted. The resulting prolongation in treatment time allows the partially depopulated cancer to divide and grow and leads to a reduction in therapeutic effect. To avoid the overlapping toxicity that occurs during the concurrent administration of chemotherapy and radiation, many trials have been designed that have tested the sequential administration of these two adjuvant modalities. Thus far none of these trials has unequivocally proven the value of chemotherapy in addition to surgery and irradiation for intact or resectable cancers of the head and neck.⁴⁻¹⁰ Ability to protect mucous membranes from the acute effects of ionizing radiation and/or cytotoxic agents would reduce the dose-limiting toxicity of these two modalities and represent a therapeutic gain in the combined modality treatment of head and neck cancer.

Most patients with head and neck cancer have a functioning gastrointestinal tract and can be nutritionally supported by enteral or parenteral feeding when an acute mucosal reaction due to radiation and or drugs is unavoidable and relatively severe. Nasogastric intubation is the simplest way of bypassing the acutely effected mucosa and delivering enough food and fluids to support the host. Esophagostomy is an alternative method that is seldom used because of the reported complication of carotid artery exposure and rupture. When prolonged nasogastric intubation is required as is the case after resection of the tongue or the pharyngeal musculature gastrostomy is preferred. Percutaneous endoscopic gastrostomy is an attractive alternative that is now accomplished on an outpatient basis. Total parenteral nutrition (TPN) is another alternative that has proven effective in maintaining nutrition during irradiation of the upper alimentary tract. Despite the proven value of TPN, enteric feeding is less complicated, cheaper and suffices for the majority of head and neck cancer patients who have an intact and functioning intestine.

Strategies to reduce the incidence and severity of acute radio mucositis include the use of antimicrobial and antifungal agents as well as thiol and prostaglandin radioprotectors. The use of chlorhexidine,¹¹ sucralfate¹² and benzydamine hydrochloride¹³ oral rinses for prevention of radiation induced oral and pharyngeal mucositis have been tried but only benzydamine hydrochloride has been shown to reduce the severity of mucositis when compared with placebo. Epstein reported a reduction in mucositis severity from a score of 3.2 ± 0.51 for eighteen placebo patients to 2.20 ± 0.56 for the 25 benzydamine hydrochloride patients ($P=.01$).¹³ Antimicrobial agents benefit but a few patients who develop a confluent exudative ulceration of the mucous membranes during irradiation. A far more common problem is the early appearance of a burning sensation and beefy red mucosa with or without the gray white plaques characteristic of candidiasis. Yeast can be documented by KOH smears or culture in roughly one quarter of patients undergoing irradiation for head and neck cancer and successfully treated with topical antifungal agents. Antimicrobial and antifungal agents successfully treat superimposed bacteria or fungal infection but do little to protect mucous membranes from the acute effects of irradiation.

To date, two effective classes of compounds have been identified that protect normal tissues from the effects of radiation, the aminothiols and prostaglandins. The aminothiols are sulfhydryl compounds that protect from the effects of ionizing radiation mainly by scavenging free radicals. Charged with protecting military and civilian populations from radiation or chemical warfare the Defense Department¹⁴ undertook an extensive program to develop thiol radioprotectors based on the early work of Patt,¹⁴ and Bacq and Herve.¹⁵ The most effective radioprotector proved to be S-2-(3-amino-propyl amino)-ethyl phosphorothioic acid (WR-2721). WR-2721 has proven radioprotective for a variety of normal tissues but its clinical usefulness has been limited by nausea, vomiting and hypotension.¹⁶ Consequently, attention has turned to the prostaglandins which are potentially more useful because they are protective

in minute quantities, can be applied topically with minimal morbidity and protect cells from the effects of cytotoxic drugs as well as radiation.

Three of the most extensively studied prostaglandins are misoprostol, 16,16 DM PGE₂,¹⁷ and iloprost.¹⁸⁻²⁰ Of these, misoprostol, a synthetic prostaglandin E₁ analog (*G.D. Searle & Company*) has proven the most radioprotective. Misoprostol consistently increases clonogenic cell survival of the small intestine to about 600% of control when 15 Gy is delivered to the mouse one to two hours after administration of misoprostol in microgram quantities (*Fig. 2*).

Figure 2

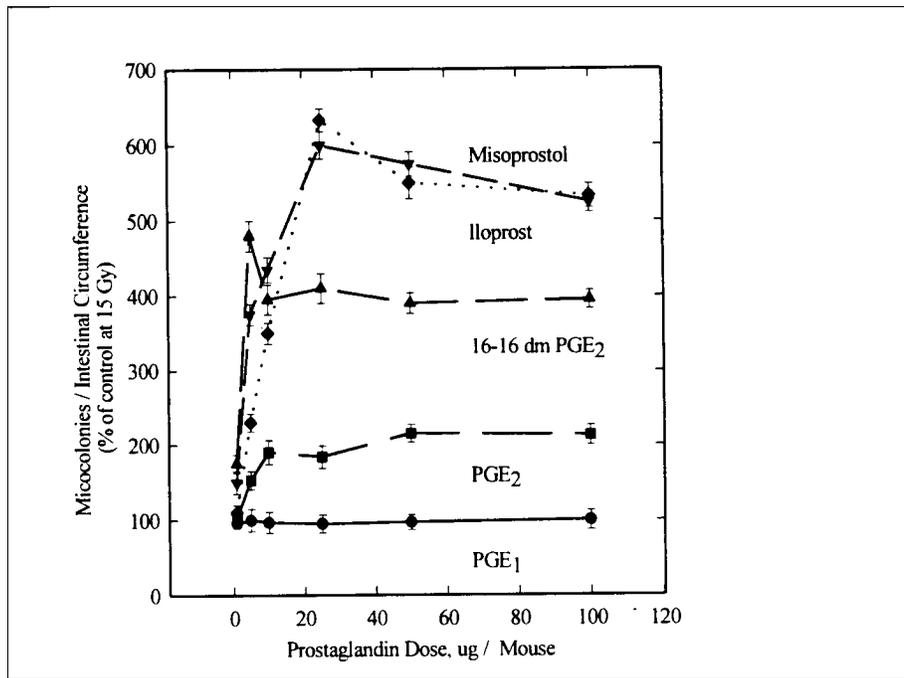
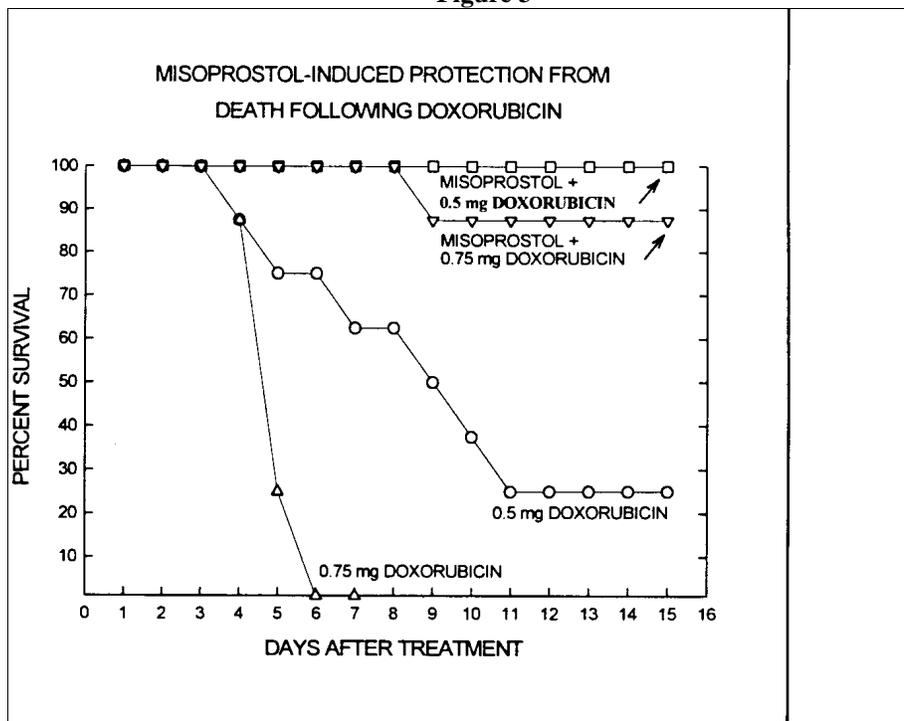


Figure 3



Misoprostol consistently exerts *in vivo* radioprotection of gut, bone marrow and hair follicles²¹ and protects these same tissues to some degree from the effects of doxorubicin (Fig. 3), cytoxan, methotrexate, etoposide and mitomycin C. It does not protect rapid cell renewal systems from 5-FU, ARA-c, hydroxyurea, or cisplatin, but there is mounting evidence that it does protect oral and pharyngeal mucosa from the effects of fractionated irradiation.²² Radioprotection even in the absence of 5-FU chemoprotection would reduce the severity of mucositis and represent a gain in the combined modality treatment of head and neck cancer.

A double-blind placebo controlled trial was recently completed at our institution to determine if misoprostol was radioprotective for oral and pharyngeal mucosa. An oral rinse containing misoprostol or placebo was administered to each patient approximately 20 minutes before each dose of external

irradiation which was fractionated at the rate of 2 Gy per day over 5-7 weeks to total doses of 50-70 Gy. Thirty four patients from the Hines VA Medical Center and thirty five from the Loyola University Medical Center were accrued to the study over a two-year period. After three weeks the 17 misoprostol patients irradiated at Loyola had significantly less mucositis ($P < .01$, *analysis of variance*) than did the 18 placebo patients, while the 17 misoprostol patients irradiated at Hines had more severe mucositis than the 17 placebo patients (*Fig. 4*).²²

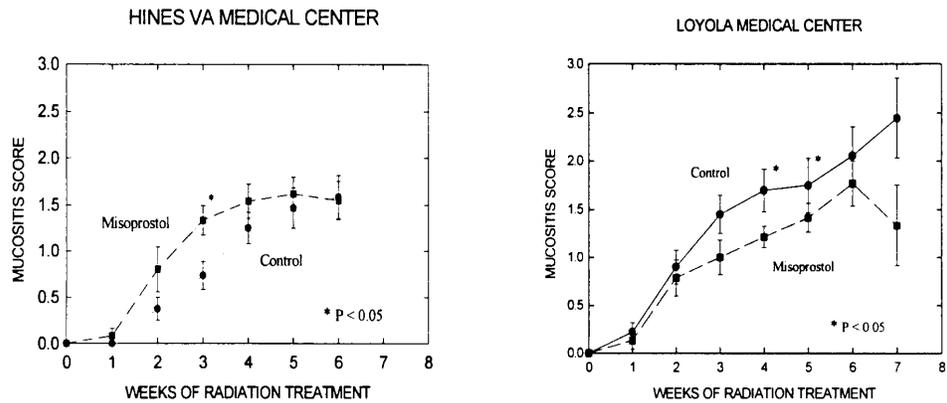


Figure 4

The difference in outcome between the hospitals is unknown but is thought to be related to poor compliance in administration of the oral and pharyngeal rinse to the patients at Hines. Given the *in vivo* protection from ionizing radiation so consistently noted in animals for a variety of rapidly dividing cell renewal systems, it is important to repeat this study to determine if misoprostol is an effective radioprotector for oral and pharyngeal mucosa.

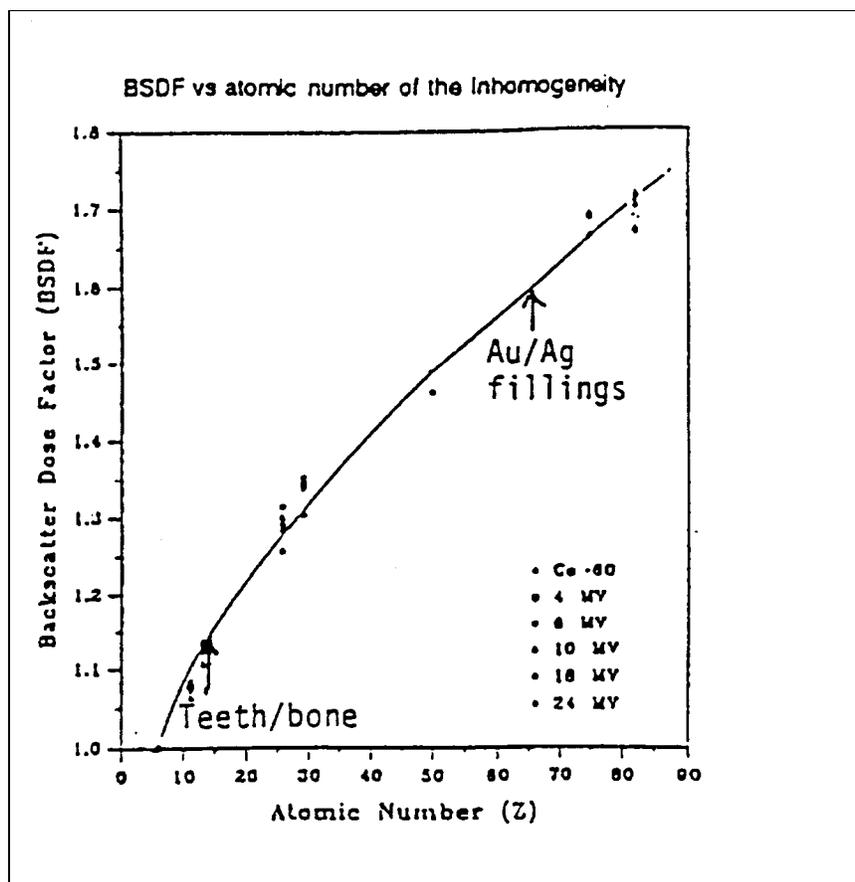


Figure 5

During the conduct of the study, some problems in the objective measurement of mucositis and timing of misoprostol administration were identified that need to be more tightly controlled in a repeat trial. A variety of radio mucositis scoring systems have been published all of which show a gradual increase in severity of mucosal reaction during the last three to four weeks of a six to seven week course of fractionated irradiation.²³ Most of these systems rely on a global assessment of radiation effects on the mucosa, but mucosal reactions were noted in some locations of the oral cavity or pharynx and not in others. For instance, it was not uncommon to see ulceration of the lateral margin of the tongue adjacent to teeth containing metallic fillings with minimal reaction elsewhere in the oral cavity and pharynx. The ulceration of the tongue was probably due to an excessive amount of radiation scattered from the metallic fillings (*Fig. 5*).^{24, 25} Some patients also had a rather severe pharyngitis with minimal reaction in the oral cavity suggesting that they did not gargle and coat the mucous membranes in the pharynx as effectively as those in the mouth. As a result of these observations, it is important to evaluate the mucosal reaction separately for the tongue, buccal mucosa, palate and pharynx. The interval between administration of the topical rinse and irradiation is also important and needs to be more tightly controlled than it was in this initial trial. In most experimental systems studied to date (*Fig. 6*), maximum radioprotection occurs when radiation is delivered one to two hours following administration of misoprostol.²² In the trial just concluded, intervals of 20 minutes or less were not infrequent. Consequently, the interval between topical administration of misoprostol and irradiation has been changed from 30 to 120 minutes in the design of this study.

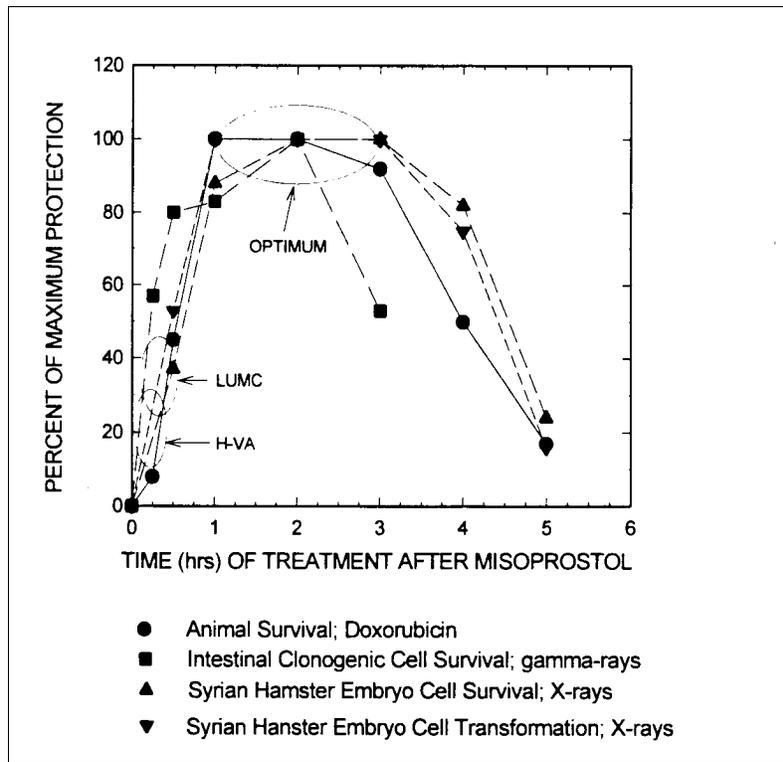
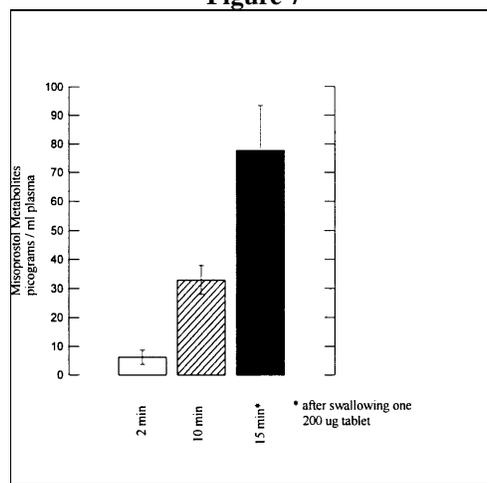


Figure 6

The possibility that misoprostol or other protective prostaglandins used in clinical settings would be absorbed in sufficient quantities to protect tumors has been a major concern. Consequently, absorption studies were conducted in healthy volunteers as part of the initial clinical trial and animal studies were undertaken to determine if misoprostol protected tumors from the effects of irradiation. Absorption of misoprostol as measured by radioimmunoassay of metabolites in the plasma of healthy volunteers was found to increase with time after four minutes of topical rinse with a 200 mcg tablet in 15 cc of water. At 10 minutes after the topical rinse misoprostol metabolites in picograms per milliliter of plasma were one half the peak level measured at 15 minutes after ingestion of a 200 mcg tablet (*Fig. 7*).²² Since transmucosal absorption of misoprostol was so great it was decided that patients in this trial should swish, gargle and swallow the compound in case systemic levels of the drug contribute to mucosal radioprotection along with topical application.

Figure 7



A critical potential problem regarding the clinical utility of PGs to protect normal tissue during cancer

therapy is their potential protective effect on tumor tissue. Thus far the ability of misoprostol to protect tumors *in vivo* from radiation has been studied in four different animal tumor models: the M-5076 ovarian sarcoma, the Lewis lung carcinoma, the Fibrosarcoma (FSa) and New Fibrosarcoma (NFSa) tumors. The latter two tumors are sarcomas that have been developed and widely studied in the Department of Experimental Radiotherapy at M.D. Anderson Tumor Institute in Texas. In collaborative studies conducted at Loyola and M.D. Anderson, misoprostol has not altered the effects of radiation on any of the four tumors as measured by regression and regrowth. Data are shown in Figure 8 for the FSa tumor.

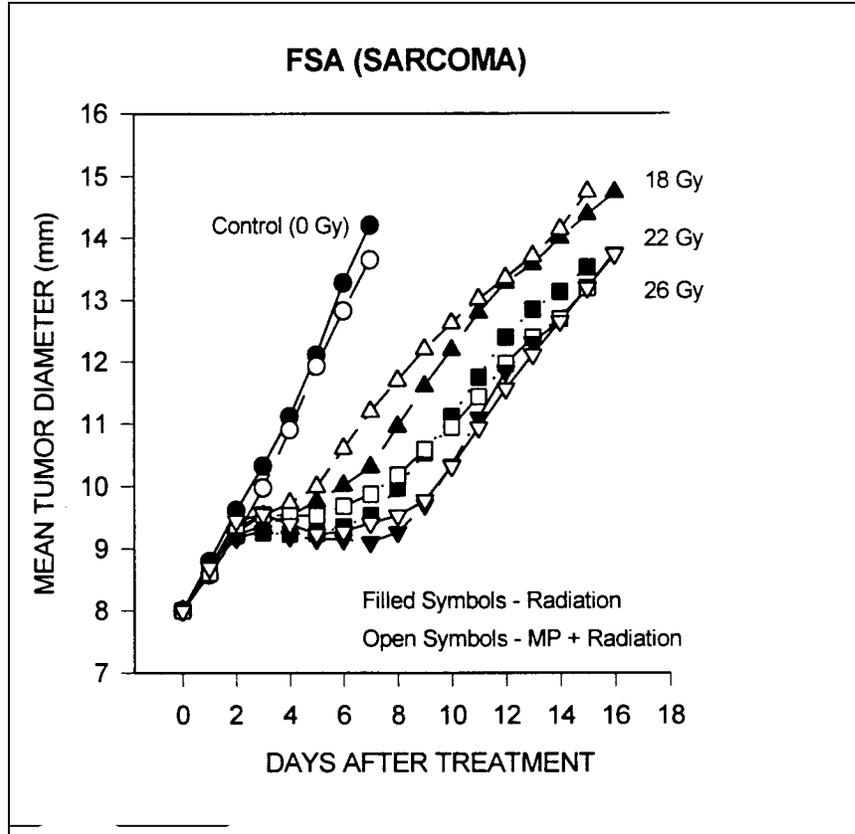


Figure 8

The single dose of radiation to locally control 50% of FSa tumors was 42 ± 4 Gy. The tumor control dose in misoprostol treated, FSa bearing mice was 43 ± 4 Gy. To investigate if tumors may be producing sufficient PGs or other factors that might negatively influence misoprostol-induced protection distant from the tumor, studies of misoprostol-induced protection of intestinal crypt clonogenic cells were conducted in mice bearing the M-5076 ovarian sarcoma. Four days after 14.5 Gy, there were 16.5 ± 2.1 microcolonies per intestinal circumference in normal mice. A similar number of microcolonies (15.6 ± 2.0) was found in tumor-bearing mice irradiated with 14.5 Gy. There were 39.6 ± 4.1 colonies in tumor-bearing mice given misoprostol 2 hours before 14.5 Gy. We conclude from these studies that tumors, for which we can find no misoprostol-induced protection, do not produce factors that negatively influence normal tissue protection distant from the tumor. Although the reasons for the lack of protection in tumors compared to normal tissue in this set of studies is unknown, there are two possibilities: 1) tumors may not have normal receptors or normal second messenger systems for the transmission of the prostaglandin signal which is translated into protection or, 2) tumors, known to produce excessive prostaglandins and leukotrienes, may have their receptors filled by their own eicosanoids and thus, exogenous prostaglandins have no protective effect locally on tumor

tissue. These data suggest that it is reasonable to proceed cautiously with a trial on patients with early stage tumors despite the fact that absorption studies indicate significant plasma levels with time after topical administration.

To treat cancer better, one can either find ways to increase the sensitivity of tumors or to differentially protect normal tissues. Hypoxic cell synthesizers have received predominant attention over the last two

decades with little clinical attention to differential radioprotection or chemoprotection of normal tissues.²⁶ The prostaglandins are especially attractive since they have proven so effective in protecting a variety of normal tissues from the effects of radiation and chemotherapy. Their cytoprotective effects are enhanced by the addition of WR-2721^{27, 28} and they are very well tolerated by the host since they can be given in microgram instead of milligram quantities. This trial has been designed to determine if misoprostol protects oral and pharyngeal mucosa from the effects of radiation.

1.2 Quality of Life Background

Quality of Life within RTOG trials is defined as follows: 1) the ability to perform everyday activities in physical, psychological, and social domain of life, and 2) patient satisfaction with levels of function as well as control of disease and/or treatment -related symptoms.²⁹ The objectives for measuring QOL outcomes in clinical trials are twofold: 1). to obtain information useful to improving treatment procedures and 2). the collection of information to evaluate which of several treatments gives better results for the majority of patients.³⁰ While the clinician's primary concern of cancer treatment is tumor control, an increasing awareness of the effective management of patients should include addressing their total "well-being".³¹ Opinions vary as to whether patient self-assessment is necessary, or if physician assessment is sufficient to determine the patient's quality of life. In several trials there seemed to be little agreement between physician assessment and the patient's own assessment of total quality of life.³²⁻³⁴ Quality of Life Dimensions are subjective, so it would seem that the patient could better assess his/her overall quality of life.^{35,36}

Cancers in the head and neck region affect some of the most fundamental functions, such as breathing, eating and speaking.^{37,38} Oral complications almost always occur as a consequence of therapeutic intervention for head and neck cancer, and becomes a significant dose-limiting toxicity of cancer therapy.³⁹

There is little accurate documentation, from the patient's point of view, as to their physical and psychological difficulties due to radiation therapy treatments. Such early documentation is necessary in reducing the negative impact of a patient's quality of life on prolonged survival.⁴⁰ In this study, one objective is to determine if the topical oropharyngeal rinse and ingestion of misoprostol protects mucus membranes from the acute effects of irradiation, with the goal of reducing morbidity and allowing for the total dose of radiation to be delivered safely and timely. The acute effects on mucosa include dysphagia, eating problems (*i.e. mastication, taste alterations*), weight loss, and salivary gland dysfunction.⁴¹ The combination of the effects of disease and the individual's ability to perform appropriately with eating and speaking. This can further lead to significant dysfunctions in a wide range of behaviors from social and family interactions to more internalized feelings of self esteem and confidence.³⁷ Thus, it will not only be important to measure and grade the physical effects on the oral mucosa, but to collect and measure the actual impact on patient's quality of life as a result of this intervention. (1/21/98)

2.0 OBJECTIVES

- 2.1 To determine if topical oropharyngeal rinse and ingestion of misoprostol protects mucous membranes from the acute effects of irradiation.
- 2.2 To evaluate QOL outcomes of patients receiving misoprostol.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 Patients who have biopsy-proven intact squamous cancers of the oral cavity, oropharynx, supraglottic larynx, or hypopharynx, or nasopharynx, T1-T2, N0-N1 clinical staging.
- 3.1.2 Patients with completely resected margin-negative cancers of the oral cavity, oropharynx, supraglottic larynx or hypopharynx T1-T3, N0-N1.
- 3.1.3 The pathologist shall verify by light microscopy that margins of excision are free of cancer and that the primary cancer does not extend closer than 5 mm from the margin of excision. Pathologist will also be sure that no more than one lymph node contains cancer and that it measures ≤ 3 cm in diameter.
- 3.1.4 Patients who will receive doses of 60 to 70 Gy, over 6 to 7 weeks, 2 Gy per day to the oral cavity, pharynx or both. Radiation must begin within 6 weeks after surgery, if performed.
- 3.1.5 Patients must be 18 years old or older.
- 3.1.6 KPS ≥ 60 .
- 3.1.7 Patients must sign a study-specific informed consent form.

- 3.1.8 Women of child-bearing age must not be pregnant (*must have a negative pregnancy test within two weeks prior to study registration*). Both men and women with reproductive potential are encouraged to use efficient contraception during treatment.

3.2 Ineligible Patients

- 3.2.1 Patients who have had previous head and neck irradiation.
3.2.2 Patients who are unable to gargle, swish, and swallow the study agent.
3.2.3 Patients who are receiving or who have had previous chemotherapy.
3.2.4 Patients receiving chlorhexidine, sucralfate or benzyhdramine hydrochloride during irradiation.
3.2.5 Patients with previous head and neck cancer, or other malignancy, except skin cancer. Locally excised T1 N0 cancer NED after 2 years is eligible.
3.2.6 Patients accessioned to other clinical protocols using RT or chemotherapy.
3.2.7 Patients with known hypersensitivity to misoprostol (*Cytotec*) or other prostaglandins.
3.2.8 Patients eligible for RTOG 95-01.

4.0 PRETREATMENT EVALUATION

- 4.1 Complete history and physical examination including KPS, weight loss prior to treatment and concurrent non malignant diseases and medications.
4.2 Assessment of alcohol and tobacco use.
4.3 Dental evaluation and diagram of remaining upper and lower teeth being careful to indicate those with metal fillings. Evaluation may be done by a dentist, oral surgeon, or radiation oncologist.
4.4 Body weight before irradiation
4.5 Presence or absence of a feeding tube
4.7 Use of analgesics, antibiotics or antifungal agents
4.8 Pregnancy test and counseling on the use of effective contraception in women of childbearing potential.
4.9 QOL baseline assessments.

5.0 REGISTRATION PROCEDURES (1/21/98)

- 5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:
- Institution Name & Number
 - Patient's Name & ID Number
 - Verifying Physician's Name
 - Eligibility Criteria Information
 - Stratification Information
 - Demographic Data
 - If treated with prior resection
 - Treatment Start Date
- 5.2 Patients receiving post operative treatment will be assigned to Option 1. Those without prior resection will be assigned to Option 2 (*there is no difference between treatment options*).

6.0 RADIATION THERAPY

6.1 Physical Factors

- 6.1.1 Equipment: Cobalt-60 machines or linear accelerators that produce megavoltage X-rays and electrons should be used.
6.1.2 Treatment distance must be ≥ 80 cm SSD or SAD for isocentric techniques.
6.1.3 Blocks: Shaped fields using Cerrobend blocks are recommended.
6.1.4 Compensating or wedge filters: The use of compensating or wedge filters should be considered to assure dose homogeneity throughout the irradiated volume.

6.2 Localization Requirements (5/13/98)

- 6.2.1 Simulation: Simulation of all fields after proper immobilization of the patient is mandatory. The investigator will send the simulation and treatment machine portal films of each field together with the prescription of treatment to RTOG headquarters for quality assurance review.
6.2.2 Verification: Portal films must be taken at least every two weeks to verify reproducibility of setup. They must also be taken at any time there is alteration of setup.

6.3 Target Volume

- 6.3.1 Mucosal sites: Radiation portals must include two or more mucosal sites, eg. pharynx and palate or

buccal mucosa and tongue.

- 6.3.2** Technique: Oral cavity, pharynx or oral cavity and pharynx must be irradiated with opposed photon portals. Oblique oral cavity portals to spare one parotid are acceptable. Wedge-pair techniques that spare mucosa on one side will not be acceptable except when used to boost the primary tumor after delivery of a minimum of 60 Gy in 6 weeks to mucosa. The upper lateral radiation portals should include the primary cancer with a minimum of 2-3 cm margin and regional lymph nodes. The low-neck field should abut the inferior margin of the upper lateral fields on the skin using a beam splitter or assymetric jaws to prevent upward divergence of the low-neck field and overlap on the spinal cord. The spinal cord must be shielded at the junction of the low-neck and upper lateral fields by using an AP midline block, 2 cm wide on the skin, in the low-neck field or by using a 2 cm high block in the posterior inferior part of the upper lateral field. The upper lateral field should be reduced to shield the spinal cord after 40-44 Gy in 4 1/2 weeks. The neck posterior to the reduced portal should be irradiated with appropriate electron beam energy (6-9 MEV) to a minimum dose of 50 Gy in 5 weeks.

6.4 Dose Calculation

- 6.4.1** Dose: Calculated to the midplane of central axis for the upper lateral fields to deliver 60-70 Gy over 6 to 7 weeks to the oral and/or pharyngeal mucosa, 2 Gy per day for 30-35 fractions. Calculated to 3 cm deep in tissue along central axis of the AP low neck field to deliver 46 Gy in 4 1/2 weeks, 2 Gy per day for a total of 23 fractions.
- 6.4.2** Weighting: Beams should be opposed and equally weighted to avoid any disparity in mucosal reaction that might result from unequal weighting of radiation beams.
- 6.4.3** Dose Distribution: Variation in dose throughout the target volume should not exceed 10% of the central axis midplane dose. A central axis distribution of radiation dose that clearly depicts a target volume should be submitted to RTOG headquarters for review.
- 6.4.4** Fractionation: Radiation will be delivered in increments of 2 Gy per day to avoid any change in mucosal reaction that might result from daily fractions less than or greater than 2 Gy per day.

7.0 DRUG ADMINISTRATION (IND#54,684) (1/21/98)

- 7.1 Preparation and Administration**: Each dose will be prepared by crushing one tablet into a dose cup, adding 15cc of purified or distilled water, and stirring thoroughly. The solution should be prepared five minutes before use. The patient will swish and gargle the misoprostol solution for 3-5 minutes and then swallow it 120 minutes before irradiation. The interval between rinse, ingestion and irradiation can vary \pm 15 minutes. It is important that the patient be present in the department two hours before the first radiation treatment in order to be instructed on how to dissolve the tablet, how to swish, gargle, and swallow the solution. At that time the patient will also be instructed on how to self-administer the misoprostol at home and how to record the time of administration on the patient diary. The patient will return the patient diary to the radiation therapy technologist to record the time of irradiation each day.

- 7.2 Misoprostol (Cytotec)**: Misoprostol a synthetic prostaglandin E₁ analogue developed by Searle for the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcers. For this study, misoprostol will be supplied in 200 ug tablets to be dissolved in water.

- 7.2.1 Side Effects**: Misoprostol is contraindicated in those with history of allergy to prostaglandins and in pregnant women because it can cause miscarriage and excessive bleeding. Diarrhea is a common side effect that ranges from 14-40% in patients on NSAID's with a daily dose of 400-800 mcg of misoprostol (average incidence in 5000 patients was 13%). Abdominal pain has been observed in 7% of patients which is not consistently different from placebo. Ulceration of the tongue and/or severe pharyngitis can occur if gargle is done improperly.

No effect (*other than a rarely encountered allergic response*) is expected with a daily rinse and ingestion of 200 mcg of misoprostol.

- 7.2.2 Absorption**: Absorption of misoprostol as measured by radioimmunoassay of metabolites in the plasma of healthy volunteers increases from 2 to 10 minutes after four minutes of oral topical rinse with a 200 mcg powder in 15cc of water. At 10 minutes after the topical rinse misoprostol metabolites in picograms per ml of plasma are half the level measured at 15 minutes after ingestion of a 200 mcg tablet.

7.3 Supplier and Distribution (11/17/97, 4/30/99)

- 7.3.1** Searle will provide misoprostol in 60 tablet bottles to Biologics, Inc. for patient-specific distribution.
- 7.3.2** Following study registration of each patient, Biologics will send one bottle by overnight mail to the person designated on the Pharmacy Registration Form in Appendix VII.
- 7.3.3** Each bottle will include the protocol number, patient number, expiration date, storage requirements and all necessary information required by Federal Regulations. Dose preparation and administration

information will also be provided on the labeling. Labels will be computer generated for this study and will be attached to the container.

7.3.4 Patients will be instructed to use the rinse only on days of irradiation and to return all unused tablets in the original bottle to their physician. The investigator will count the remaining tablets, subtract from the original 60, and will record the difference on the data collection forms and in the patient's department record.

7.3.5 Unused tablets will be shipped to:

**Clinical Pharmacy
G.D. Searle
4901 Searle Parkway
Skokie, IL 60091**

7.3.6 If there are any questions, call Neli Gioffreda at (847) 506-8740 at the Searle Pharmacy (FAX # 847-506-8761).

7.4 Adverse Drug Reaction Reporting

7.4.1 The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol which uses commercial agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days:

7.4.1.1 Any ADR which is both serious (*life threatening, fatal*) and unexpected.

7.4.1.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature.

7.4.1.3 Any death on study if clearly related to the commercial agent(s).

7.4.2 The ADR report should be documented on Form FDA 3500 (*Appendix V*) and mailed to the address on the form, to RTOG Headquarters and to:

**Investigational Drug Branch
P.O. Box 30012
Bethesda, MD 20824
Telephone (301) 230-2330
available 24 hours
fax 301-230-0159**

8.0 SURGERY

8.1 Surgical excision of the primary tumor should be accomplished with a minimum of 5 mm margin by light microscopic examination. When indicated, excision with frozen section control is advised to achieve negative margins. The operation selected will depend on the site of the primary tumor and may vary from conservative to radical depending on the size of the primary tumor. All forms of excisions are acceptable as long as negative margins are achieved; these include local excision by cold knife or laser, pull-through excision, compartmentectomy, and en-block excision of tumor and involved anatomy.

8.2 Modified or radical neck dissection or limited excision of lymph nodes may be done for patients without palpable lymph nodes or those with a single lymph node less than 3 cm in diameter.

9.0 OTHER THERAPIES

9.1 Topical anesthetics, antibiotics, and antifungal agents may be used to alleviate the pain and discomfort of radiomucositis.

9.2 Record all agents on the data collection forms.

10.0 PATHOLOGY

No central review is planned for this study

11.0 PATIENT ASSESSMENTS

11.1 Patient Evaluation

	<u>Pre Rx</u>	<u>During Rx</u>	<u>At Followup</u> <u>See Section 12.1</u>
Complete history, P&E	X		X

KPS and weight	X	X ^c	X
Biopsy	X		X ^a
Alcohol and Tobacco Use	X		X
Dental Evaluation and Diagram	X		
Pregnancy Test	X ^b		
Toxicity Evaluation		X ^c	X
QOL Assessment	X		X ^d
Metastatic Evaluation	X		X ^b

- a. for confirmation of recurrent tumor in the head and neck as applicable
- b. as applicable
- c. weekly
- d. see Section 11.6.1

11.2 Mucosal Reaction

11.2.1 Objective Scoring: Visual signs of radiation mucositis will be independently assessed once weekly by the radiation oncologist using the RTOG scoring system (*Appendix IV*). Separate assessments of those areas being irradiated, the pharyngeal wall, palate, buccal mucosa and lateral margin of the tongue will be made.

Acute Effects of Radiation

Grade	Signs
0	No reaction
1	injection (<i>erythema</i>), mild pain, no analgesics
2	patchy mucositis, moderate pain, ± analgesics
3	confluent mucositis, severe pain, ± narcotics
4	ulceration, hemorrhage, necrosis

11.3 Body Weight: Will be measured before and once weekly during irradiation to assess nutritional intake.

11.4 Medications: Use of antibiotics, antifungal agents and analgesics for oral or pharyngeal pain will be recorded before and once weekly during irradiation.

11.5 Treatment Interruption: Any interruption of radiotherapy for whatever reason, pain, machine malfunction, inter- current illness, lack of transportation or social obligation will be recorded.

11.6 Quality of Life

11.6.1 Two patient administered questionnaires have been selected. The components of the two questionnaires include four domains of QOL, head and neck symptom-specific items and questions about the patient's current use of alcohol and tobacco. Because of the different focus of this study (*intervention vs. disease outcome*) the QOL assessments will include a baseline assessment, week 6 during RT, and at 3 months from start of RT.

11.6.1.1 The first questionnaire was developed by Weymuller, et al. of the University of Washington, Seattle.⁴² This questionnaire was designed specifically to address problems incurred by head and neck cancer patients. The University of Washington QOL questionnaire was tested on 75 head and neck patients. The questionnaire was compared to two established tools, the Karnofsky and the Sickness Impact Profile (*SIP*), for validity, acceptability, reliability and responsiveness. The overall results demonstrated the U of W H&S tool to be equivalent to the Karnofsky and SIP for reliability, responsiveness, and was preferred test format for 97% of the tested patients. The selection of the U of W QOL tool is for its reference to specific symptom-related effects (*saliva, eating, taste, swallowing*) of the intervention of misoprostol. The scale consists of seven symptom-specific categories (*disfigurement and speech were omitted for this study because these areas are not affected by the intervention of the misoprostol*) each describes important daily living dysfunctions/limitations of head and neck cancer and the treatment outlined for this study. Each category has five possible item choices. The highest level or "normal is scored 100 points while the lowest (*or greatest dysfunction*) is scored 0 points. The options between are in multiples of 25. The patient is asked to circle the statements which best describes their current status. The scores are totaled then divided by 7 to obtain the final range. The higher the score the greater the QOL and conversely, the lower the score the lower the QOL.

11.6.1.2 The second measure used in this study will be a very brief questionnaire addressing Tobacco use,

Alcohol use, and Diet Assessment. This aspect of the study is exploratory, in order to describe the impact of alcohol, smoking and diet behaviors on toxicity, survival and second cancers. It has been reported that smoking cigarettes during radiotherapy prolongs the period of reaction and may reduce the chance of cure.⁴³ There is also growing evidence that smoking cessation at diagnosis may prolong survival, either directly or by reducing second malignancies in patients with head and neck cancer.⁴⁴

11.6.2 Non English speaking patients may participate in these studies through a translator.

12.0 DATA COLLECTION

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 2 wks of study entry
Initial Evaluation Form (I1)	
Diagnostic Pathology Report (P1)	
+ Primary Site Staging Worksheet (I6)	
+ Nodal Site Staging Worksheet (I7)	
* Surgery Form (S1)	
* Surgery Report (S2)	
* Surgical Pathology Report (S5)	
Pretreatment Symptom Scale Questionnaire (QL)	
Pretreatment Tobacco, Alcohol, Diet Questionnaire (PQ)	
Study Specific Flowsheet (SF)	Within 1 week of RT end
Radiotherapy Form (T1)	
<u>Final Dosimetry Information:</u>	
Daily Treatment Record (T5)	
Isodose Distribution (T6)	
Calculation Data Form for All Fields (TL)	
Supplementary Films for All Fields (TP)	
<i>(simulation and portal)</i>	
Followup Symptom Scale Questionnaire (SS)	At 6 and 13 weeks from RT start.
Followup Tobacco, Alcohol, Diet Questionnaire (PF)	
Tissue Reaction Form (F2)	Upon completion of week 13 assessment
Study Specific Flowsheet (SF)	
The Patient Diary is included with the forms packet for institutional use, not for submission to RTOG.	
+ Disease status at diagnosis	
* Due if resection was performed prior to study entry.	

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 The primary endpoint of this trial is the acute mucositis in the pharynx, palate, tongue, or buccal.

13.1.2 Quality of life as measured using the University of Washington Head and Neck Symptom questionnaire

13.2 Sample Size

13.2.1 Mucositis Endpoint

The primary endpoint of this trial is the incidence of acute radiation mucositis. The RTOG head and neck database contains more than 2000 patients treated with radiation therapy and no chemotherapy. In this database the incidence of acute radiation mucositis is:

Grade of Mucositis				
0	1	2	3	4
14%	22%	45%	18%	1%

This is the worst severity observed in either the the pharynx, palate, tongue, or buccal within 90 days from the start of radiotherapy. Toxicity data is ordered categorical, and Whitehead’s sample size formula for this type of data was employed.⁴⁹ Assuming that the application of misoprostol during radiotherapy reduces the incidence of grade 3 and 4 mucositis by 50%, we can estimate all probabilities as follows:

Estimated Incidence on the Misoprostol Arm				
Grade of Mucositis				
0	1	2	3	4
28%	29%	34%	9%	0%

Setting the significance level at 80% and statistical power at 90% the estimated sample size is 29 patients. Assuming a 10% ineligibility/inevaluability rate, the **total sample size required is 32 patients.**

13.2.5 Patient Accrual

The following table displays the length of time necessary to accrue 32 patients given different average monthly accruals.

<u>Average Monthly Accrual</u>	<u>Time to Accrue 32 Patients</u>
12.0	3 months
10.0	4 months
8.0	4 months
6.0	6 months

The average monthly accrual is expected to be 6-8 patients per month, thus it will take 4-6 months to complete the accrual phase of this study. However, if the monthly accrual is less than 3 patients per month the feasibility will be re-evaluated.

13.3 Analysis Plans

13.3.1 Interim Analyses of Accrual and Toxicity Data

Interim reports with statistical analyses will be prepared every six months until the initial paper reporting the treatment results has been submitted. In general, the interim reports will contain information about:

- a) the patient accrual rate with projected completion date for the accrual phase;
- b) the distribution of patients with respect to pretreatment characteristics, including the participation rates of women and minorities;
- c) compliance rate of treatment delivery with respect to the protocol prescription;
- d) the frequency and severity of the toxicities.

13.3.3 Analysis and Reporting of Initial Treatment Results

The major analysis will be undertaken when each patient has been potentially followed for a minimum of three months. The usual components of this analysis are:

- a) tabulation of all cases entered and any excluded from the analysis with the reasons for such exclusions;
- b) reporting institutional accrual;
- c) distribution of the important prognostic factors by assigned treatment;
- d) observed results with respect to the study endpoints.

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APPENDIX I

RTOG 96-07

A Phase II Study of Radioprotection of Oral And Pharyngeal Mucosa By the Prostaglandin E₁ Analog Misoprostol

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in my participation in clinical research so as to afford me the opportunity to make the decision whether or not to undergo the procedure after knowing the risks, benefits, and alternatives. This disclosure is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

I understand that I have been diagnosed with a tumor of the head and neck area and that further treatment is recommended. The standard treatment in cases such as mine is radiation therapy treatments given once per day, 5 days per week, Monday - Friday, for 6 to 7 weeks. Radiation therapy is a form of cancer treatment using high energy x-rays. I will be treated for my cancer with a full 6-7 week course of radiation therapy.

Radiation therapy affects some normal tissues in the area that is treated along with the cancer cells. Many patients treated to the head and neck region develop sores inside the mouth. This condition is known as radiation mucositis. It is often painful and can make it difficult to eat and drink, leading to weight loss or cause unwanted delays in the completion of my radiation therapy treatments. Previous studies have shown that gargling with a solution of misoprostol (*Cytotec*) may, in some patients, reduce the amount of mucositis caused by the radiation therapy treatments. The purpose of this study is to determine whether gargling and swallowing a solution of the drug misoprostol each day prior to radiation therapy treatments will help to reduce the amount of mucositis without adversely affecting the ability of radiation to eliminate tumor. In addition, this study will attempt to determine how I see the quality of my life.

DESCRIPTION OF PROCEDURES

The misoprostol will be supplied to me at no charge by the pharmaceutical company. I will be supplied with a bottle of 60 pills (*misoprostol*). Each day, 120 minutes (*2 hours*) prior to my radiation therapy treatment, I will crush one pill into a small plastic cup. Then I will thoroughly stir in one tablespoon of distilled (*non carbonated bottled*) water to dissolve the crushed pill. I will gargle and swish this solution thoroughly throughout my throat and mouth for 3-5 minutes and then swallow it. To get the most benefit, it is very important to swish and gargle as directed (*2 hours before radiation ± 15 minutes*). I should prepare the solution about five minutes before I use it. I will gargle and swish only on the days I get my radiation treatments and will record the gargles on a sheet provided by my doctor. It is very important that I follow my doctor's instructions about following these procedures very closely. When my treatments are finished, I must return all unused pills to my doctor in the original bottle.

Before my first treatment and at 6 and 13 weeks after that, I will complete two Quality of Life questionnaires about how I am feeling and about any changes in my eating habits.

The radiation therapy treatments that I will be receiving are not a part of this study and will be determined by my physician based on the characteristics of my particular tumor.

RISKS AND DISCOMFORTS

Misoprostol

The possible side-effects associated with misoprostol include diarrhea (*occurred on average in 13% of 5000 patients*) and abdominal pain. Improper gargling can cause tongue sores or severe sore throat. Other reactions which have occurred in 1% to 4% of patients, but have not been proven to have been caused by the drug include nausea, gas, headaches, trouble breathing, vomiting and constipation.

Misoprostol causes miscarriages, fetal death, and menstrual disorders including severe bleeding. I understand that I cannot participate in this research project if I am pregnant. If I have (*male or female*) childbearing potential, I must use effective contraception and must have a negative pregnancy test within the last two weeks. If I do become pregnant while participating in this study, I will stop taking the misoprostol right away and contact my physician immediately.

There is also a possibility that misoprostol protects tumor from the effects of radiation but this has not been proven by live animal studies. Existing studies so far have shown that there is no tumor protection with Misoprotstol.

Radiation

The acute effects, late after effects and possible complications of radiation will be explained to me by my radiation oncologist. These might possibly include sore mouth, difficulty eating, alteration of taste, permanent dry mouth and thickening of saliva, susceptibility of teeth to decay and possible damage to jaw, larynx, spinal cord and brain.

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment will be provided by the institution which is caring for me. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. _____ the investigator in charge at _____
_____. In addition, I may contact _____
_____ at _____

for information regarding patients' rights in research studies.

BENEFITS

It is not possible to predict whether or not any personal benefit will result from the use of this treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly to help others. One possible benefit of this treatment program is less mucositis developing during treatment but I understand that this is not guaranteed.

I have been told that should my disease become worse, side effects become very severe or new scientific developments occur that indicate the treatment is not in my best interest, the treatment would be stopped. Alternative treatment would be discussed.

ALTERNATIVES

The only other clinically tested drug reported to reduce radiation mucocitis is benzadamine hydrochloride which is an alternative to participation in this study. If I choose not to participate in this study my doctors will manage any mucositis as it occurs. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research which would not otherwise be necessary. Some of these procedures may result in added costs but may be covered by insurance.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I

understand my participation has been voluntary.

CONFIDENTIALITY

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of drug manufacturers, and other groups or organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature (or Legal Representative)

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX III

American Joint Commission AJC Staging, 4th Edition 1992

AJC STAGING-Primary Tumor (T)

Oral Cavity

Buccal mucosa
Lower alveolar ridge
Upper alveolar ridge
Retromolar gingiva (Retromolar trigone)
Floor of mouth
Hard palate
Anterior two-thirds of the tongue

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*
T1 Tumor ≤ 2 cm in greatest dimension
T2 Tumor $> 2 - \leq 4$ cm in greatest dimension
T3 Tumor more than 4 cm in greatest dimension
T4 Tumor invades adjacent structures (*e.g. through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin*).

PHARYNX

Oropharynx

Faucial arch including soft palate, uvula and anterior tonsillar pillar
Tonsillar fossa and tonsil
Base of tongue including glossoepiglottic and pharyngoepiglottic folds
Pharyngeal wall including lateral and posterior walls and posterior tonsillar pillar

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*
T1 Tumor 2 cm or less in greatest dimension
T2 Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3 Tumor more than 4 cm in greatest dimension
T4 Tumor invades adjacent structures (*e.g. through cortical bone, into deep [extrinsic] muscle of tongue*)

Nasopharynx (Ineligible for this study)

Postero-superior wall
Lateral Wall
Inferior (anterior) wall, consists of the superior surface of the soft palate

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*
T1 Tumor limited to one subsite of nasopharynx
T2 Tumor invades more than one subsite of nasopharynx
T3 Tumor invades nasal cavity and/or oropharynx
T4 Tumor invades skull and/or cranial nerve(s)

Hypopharynx

Pyramidal sinus
Posterior area
Posterior hypopharyngeal wall

- TX Tumor that cannot be assessed
T0 No evidence of primary tumor
T_{is} Carcinoma *in situ*
T1 Tumor limited to one subsite of hypopharynx.
T2 Tumor invades more than one subsite of hypopharynx or an adjacent site, without fixation of hemilarynx.
T3 Tumor invades more than one subsite of hypopharynx or an adjacent site, with fixation of hemilarynx.
T4 Tumor invades adjacent structures (*e.g. cartilage or soft tissues of neck*).

LARYNX

Supraglottis

Ventricular bands (*false cords*)
Arytenoids
Suprahyoid epiglottis (*both lingual and laryngeal aspects*)
Infrahyoid epiglottis
Arytenoepiglottic folds (*laryngeal aspect*)

- TX Tumor that cannot be assessed
T0 No evidence of primary tumor
T_{is} Carcinoma *in situ*
T1 Tumor limited to one subsite of supraglottis with normal mobility.
T2 Tumor invades more than one subsite of supraglottic or glottis with normal vocal cord morbidity.
T3 Tumor limited to larynx with vocal cord fixation and/or extension to involve postcricoid area, medial wall of pyriform sinus, or pre-epiglottic tissues.
T4 Massive tumor extending beyond the larynx to involve oropharynx, soft tissue of neck, or destruction of thyroid cartilage.

Glottis

True vocal cords including anterior and posterior commissures

- TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T_{is} Carcinoma *in situ*
T1 Tumor limited to the vocal cord(s) (*may involve anterior or posterior commissures*) with normal mobility
T1a Tumor limited to one vocal cord
T1b Tumor involves both vocal cords
T2 Tumor extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility
T3 Tumor limited to the larynx with vocal cord fixation
T4 Tumor invades through thyroid cartilage and/or extends to other tissues beyond the larynx (*e.g., oropharynx, or soft tissues of neck*)

Subglottis

- TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T_{is} Carcinoma *in situ*
T1 Tumor limited to the subglottis
T2 Tumor extends to vocal cord(s) with normal or impaired mobility
T3 Tumor limited to larynx with vocal cord fixation
T4 Tumor invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx (*e.g.*

to the oropharynx, or soft tissues of the neck)

Nodal Involvement (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single ipsilateral node, 3 cm or less in greatest dimension.
- N2 Metastasis in a single ipsilateral node, more than 3 cm, but not more than 6 cm in greatest dimension or multiple ipsilateral or bilateral or contralateral nodes, none more than 6 cm in greatest dimension.
 - N2a Metastasis in a single ipsilateral node more than 3 cm, but not more than 6 cm in greatest dimension.
 - N2b Metastasis in a multiple ipsilateral nodes, none more than 6 cm in greatest dimension.
 - N2c Bilateral or contralateral lymph node more than 6 cm in greatest dimension.
- N3 Metastases in a lymph node more than 6 cm in greatest dimension.

Stage Groupings

- Stage I - T1, N0, M0
- Stage II - T2, N0, M0
- Stage III - T3, N0, M0
T1-3, N1, M0
- Stage IV - T4, N0-1, M0
T1-4, N2-3, M0
Any T, or any N, M1

APPENDIX V

ADVERSE REACTION REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires special handling, study-specific reporting procedures supercede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3214). When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone.
3. A written report containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (*in the case of RTOG-coordinated intergroup studies*) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (*grade 5*) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (*grade 4*) toxicities resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major

organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\geq *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (*IDB*)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- | | |
|---|---|
| - All deaths during therapy with the agent. | Report by phone within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working days. |
| - All deaths within 30 days of termination of the agent. | As above |
| - All life threatening (<i>grade 4</i>) events which may be due to agent. | As above |
| - First occurrence of any toxicity (<i>regardless of grade</i>). | Report by phone within 24 hours to IDB <u>drug</u> monitor and RTOG Headquarters.
**A written report may be required. |

ii. Phase II, III Studies Utilizing Investigational Agents

- | | |
|---|--|
| <ul style="list-style-type: none">- All fatal (grade 5) and life threatening (grade 4) <u>known</u> adverse reactions due to investigational agent. | <p>Report by phone to RTOG Headquarters and the Study Chairman within 24 hours
**A written report must be sent to RTOG within working days with a copy to IDB.
(Grade 4 myelosuppression not reported to IDB)</p> |
| <ul style="list-style-type: none">- All fatal (grade 5) and life threatening (grade 4) <u>unknown</u> adverse reactions resulting from or suspected to be related to investigational agent. | <p>Report by phone to RTOG Headquarters, the Study Chairman and IDB within 24 hours.
**A written report to follow within 10 working days.</p> |
| <ul style="list-style-type: none">- All grade 2, 3 <u>unknown</u> adverse reactions resulting from or suspected to be related to investigational agent. | <p>**Report in writing to RTOG Headquarters and IDB within 10 working days.</p> |

** See attached (if applicable to this study) NCI Adverse Drug Reaction Reporting Form

APPENDIX VI

Sample Patient Instructions

The following patient instructions may be distributed to your patients or you may substitute your own.

Patients' Initial General Instructions

Your treatment includes taking a medication (*a dissolved pill*) that you swish around in your mouth and then swallow. This medication is tasteless and odorless, and must be taken two hours before each of your radiation treatments. You can be instructed to take the medication at home or at your job before you leave for your treatment. If this is your choice, you will be given a supply of pills. Each day you are scheduled to receive your radiation treatment, you will prepare one pill. Administration instructions provided by your doctor will explain how to take the medication. A staff member in the radiation therapy department, such as a nurse, doctor or research associate will go over all instructions with you and a family member or friend. During your first few days of treatment or until you are familiar with the process, you may be given the medication in the radiation therapy department; therefore, on these days, you will need to be in the department at least two hours before you are scheduled to receive your treatment. You will be given written instructions on how to store, mix and take the medication. It is advisable to have someone other than yourself (*your spouse, a family member or friend*) listen to the instructions given to you. This will be helpful to you in case you need assistance. You will also be given some Diary Sheets for you to record the medication you take at home. The Diary Sheets contain a few questions that will be explained to you. You will also be given the name and phone number of a contact person in the radiotherapy department to call if you have questions about the information or instructions.

Storage of Medication

For safety reasons, keep all medications away from children, pets and other persons. Keep the medication dry until it is mixed. Be sure to use **ONLY THE AMOUNT** directed. The supply given to you may be enough for the entire treatment period (*approximately 35*) or you may be given just enough for a specified number of treatments, in which case, you will need to be resupplied. Be sure to request more medication if your supply is low. If you have pills left over at the time you complete all of your radiation treatments, the unused pills must be returned to the contact person in the radiation therapy department. **DO NOT** throw these out in the trash.

Preparation and Administration of Medication At Home

Medication is taken only on days you are scheduled to receive a radiation treatment. About two hours before your scheduled treatment, remove one pill from the bottle. Using a spoon or fork, crush the pill in a small plastic cup. Add one tablespoon of tap water to the medication to dissolve it; stirring until the medication is thoroughly mixed. Before taking the medicine into your mouth, note and write down the time on your Diary Sheet. The solution is then taken into your mouth but do not swallow it yet. The liquid is to be swished around in your mouth (*like using a mouthwash*) so that it comes in contact with all the surfaces inside your mouth and throat. There is no odor or taste to the liquid but you may feel a slight stinging sensation. To get the medication to the back of the throat, you will need to gargle with it. Do this before you are ready to swallow. This swishing and gargling process needs to be continued for about three minutes but not more than five minutes.

Then you swallow the liquid. This allows the remaining medication to be absorbed by your body. After you have taken the medication, rinse and dry the cup for reuse. Complete the questions on the Diary and bring it with you to your treatment each day. You must arrive in the radiation department in time to begin your radiation treatment two hours after you have taken the medication (*give or take 15 minutes*). Plan to arrive in the radiation therapy department about 20 minutes before you are scheduled for treatment and report your arrival to the technologist. This will give the technologist time to prepare for your treatment and administer it on time. If you have not taken the medication, report this immediately to the technologist, physician, nurse or contact person. If you need to see a physician before a treatment or are scheduled for an examination, take this into account when planning your medication and arrival time so that the timing of drug and treatment can be coordinated and done on schedule. On days you are scheduled to see your physician, this interview should be scheduled after your treatment so not to affect the treatment timing. Each day, be sure to have the technologist record the time of treatment in your Diary. If you forget to bring your Diary, remind the technologist to record the time of your treatment in the treatment record so your Diary can be updated at another treatment visit. Report any side effects from drug or radiotherapy to your physician. You should note this information in your Diary.

Completion of the Patient Diary

It is important that all doses of medication and the time you take each dose be recorded. Therefore, you will be given a supply of Diary sheets, one for each week of treatment and a few extras. Each day you take the medication you will write in the date under the Day of the Week. You write in the time you start the mouth rinse (*described in Administration of Medication*). After you swallow the medication, complete the other questions on the Diary for that day. The time your radiation treatment is given should be recorded by the technologist so you need to bring your Diary with you each day. If you forget to take your medication or if for some reason do not wish to take it, report this to the physician immediately when you arrive in the department. If you forget to record your treatment or do not record the time, do not try to guess but check with the contact person who can advise you. At the end of each week, turn in your Diary to the contact person. Ask questions whenever you have one.

APPENDIX VII

**PHARMACY REGISTRATION
RTOG 96-07**

Misoprostol will be mailed only to institutions who have identified a single individual for receipt of shipment. This form must be completed and returned to RTOG Headquarters prior to registering any patient on study. Allow adequate processing time (7-10 days) before calling to register your first patient.

SHIP TO:

Name: _____

Address: _____

Telephone: _____

Fax#: _____

RTOG Institution#: _____

Institution Name: _____

IRB Approval Date: _____

Investigator (PI) Signature _____ Date: _____

Investigator Name (Print) _____

Investigator NCI # _____

Send Completed Form to:

*RTOG Headquarters
1101 Market Street
Philadelphia, PA 19107*

**ATTN: ELAINE PAKURIS
FAX# 215/928-0153**

RTOG Headquarters Approval _____ Date: _____