A Randomized Study of Topical Dilute Hypochlorite (Modified Dakin's Solution) Treatment for the Prevention of Radiation Dermatitis in Head and Neck Cancer

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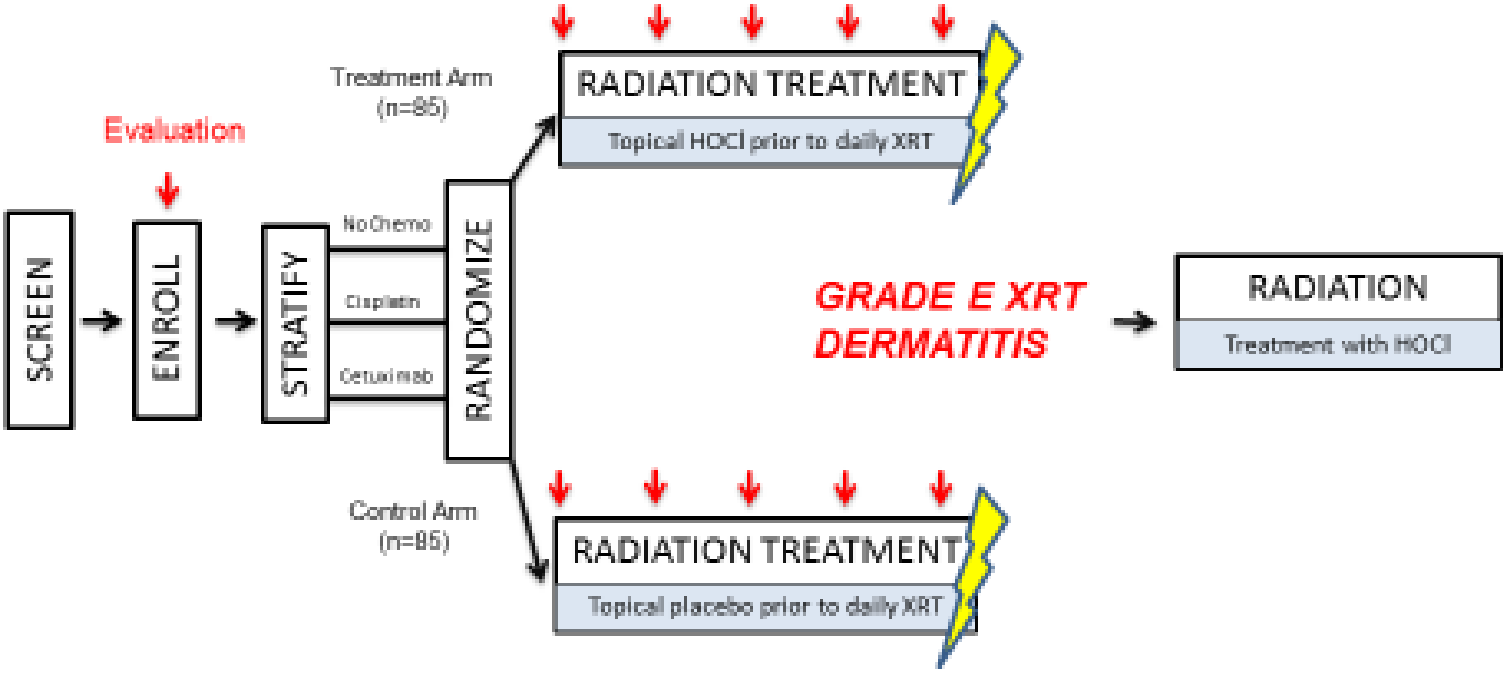
PROTOCOL SYNOPSIS

TITLE	Randomized Study of Topical Dilute Hypochlorite for the Prevention of Radiation Dermatitis in Head and Neck Cancer
STUDY PHASE	Phase III
STUDY REAGENT	1:1000 dilute hypochlorite solution (0.005%) administered to the skin prior to daily radiation therapy
PRIMARY OBJECTIVE(S)	The primary objective is to determine whether prophylactic topical dilute HOCl reduces the proportion of patients who develop Grade E radiation dermatitis as scored on the Stanford Radiation Dermatitis Scoring System (SRDSS)
SECONDARY OBJECTIVE(S)	Secondary objectives are: - To determine whether this agent delays the time to development of Grade E radiation dermatitis - To determine whether this agent improves quality-of-life and pain scores associated with radiation dermatitis
TREATMENT SUMMARY	Eligible patients will be randomized to daily application of topical dilute hypochlorite versus placebo for 10 minutes within 3 hours prior to daily radiation treatment. When patients in either arm develop Grade E radiation dermatitis during the radiotherapy course, they will be switched to topical dilute hypochlorite treatment daily per standard of care. Patients will complete the Modified Brief Pain Inventory at study entry, at 40-50 Gy through the radiation treatment course, at the end of radiation treatment, and at the follow-up visit 3-12 weeks after radiation treatment.
SAMPLE SIZE	170 Patients (85 patients per arm)
STATISTICAL CONSIDERATIONS	Sample Size Calculation: From prior clinical experience, we anticipate that 80% of patients will experience Grade E radiation dermatitis with standard skin care. In order to detect a 20% reduction in patients with Grade E dermatitis (80% vs 60% in those treated with dilute hypochlorite solution) with a two-sided alpha of 0.05 and beta of 80%, 170 patients will be enrolled. Primary endpoint: The proportion of patients in each arm who develop Grade E radiation dermatitis (as defined by the Stanford Radiation Dermatitis Scoring System) during a course of radiation therapy will be assessed using a multiple logistic regression model adjusting for type of chemotherapy (cisplatin, cetuximab, none). Secondary endpoints: Time to development of Grade E radiation dermatitis in each arm will be assessed using the Cox proportional hazards model adjusting for type of chemotherapy. QOL/Pain scores will be analyzed using a repeated measures model adjusting for type of chemotherapy.

SCHEMA


SCREEN
ENROLL
Evaluation
STRATIFY
No Chemo
Cisplatin
Cetuximab
RANDOMIZE
Treatment Arm
(n=85)
RADIATION TREATMENT
Topical HOCl prior to daily XRT
Control Arm
(n=85)
RADIATION TREATMENT
Topical placebo prior to daily XRT
GRADE E XRT
DERMATITIS
RADIATION
Treatment with HOCl

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
CRF	Case report/Record form
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
HOCl	Hypochlorite
IRB	Institutional Review Board
MBPI	Modified Brief Pain Inventory
RR	Response Rate
SAE	Serious adverse event
SRDSS	Stanford Radiation Dermatitis Scoring System

1. OBJECTIVES

1.1. Primary Objective

The primary objective is to determine the proportion of patients who develop Grade E radiation dermatitis (as defined by the Stanford Radiation Dermatitis Scoring System, See APPENDIX B) as an adverse effect of radiation therapy or chemoradiation therapy for a head and neck cancer when initiating the use of prophylactic HOCl at the start of therapy (experimental arm) compared to placebo (control arm).

1.2. Secondary Objectives

The secondary objectives include the time to development of Grade E radiation dermatitis and the quality-of-life and pain levels (as assessed by the Modified Brief Pain Inventory) in the control arm versus the experimental arm.

2. BACKGROUND

2.1 Study Disease

Radiotherapy is often used in combination with surgery and systemic therapy for the treatment of various malignancies. [1]. Although technological advances have allowed for more precision and accuracy in targeting malignant tissues, normal tissues unavoidably receive some radiation dose. For example, the skin overlying the target area receives incidental radiation, and up to 95% of patients can develop an acute reaction called radiation dermatitis [2, 3]. Radiation dermatitis develops when the skin is unable to repair itself in a timely manner upon repeated exposures to radiation [3-5]. Topical agents such as moisturizers, aloe vera, or corticosteroids can offer some relief of pain and irritation, however several randomized trials have demonstrated that they unfortunately do not prevent the onset of radiation dermatitis [1, 6-12]. For moderate-to-severe cases of radiation dermatitis, a break in the radiation treatment regimen is often required to allow time for the skin to heal. In addition to skin irritation and breakdown, patients can also experience significant pain and discomfort during this time. The only agent that has been shown in a randomized trial to significantly reduce the severity of skin reactions is a silicone dressing (Mepitel Film) [8]. While this was shown to reduce the incidence of moist desquamation in women undergoing radiotherapy treatments for breast cancer, it can cost up to $85 for a package of 10 dressings, making this type of treatment unaffordable for many patients [13]. Thus, significant improvements in the treatment of radiation dermatitis, a common side effect of radiation treatment, are needed.

For patients with locally advanced head and neck cancer, chemoradiation has become standard of care [14-19]. Cisplatin is the standard agent for concurrent therapy; however, cetuximab, a molecular inhibitor of EGFR, is used as an alternative[20]. The addition of concurrent chemotherapy to radiation treatment has resulted in increased rates of Grade 3-4 radiation dermatitis ranging from 2-35% compared to 4-21% with radiation alone[14-20]. In addition, cetuximab is notorious for its significant skin toxicity and may potentiate radiation dermatitis as well with Grade 3-4 toxicity affecting 16-60% of patients undergoing concurrent treatment with radiation[21-23].

Radiation dermatitis is typically scored using the CTCAE Scoring System. A severity of Grade 2 indicates moist desquamation that is patchy or found in skin creases while Grade 3 indicates confluent moist desquamation away from skin creases. Moist desquamation in the head and neck region causes significant morbidity for patients: pain at the neck leading patients to alter their clothing at the neck line, inability to shower, lack of restful sleep, discomfort while eating, and feeling self-conscious when

being seen in public. There are multiple treatments for this complication, but practice varies by institution, and there is no established standard of care.

2.2 Study Agent and Rationale

A standard treatment for radiation-induced moist desquamation (regardless of Grade 2 or Grade 3 scoring by CTCAE) is dilute hypochlorite applied topically once or twice daily to the affected area. In this context, this treatment is given primarily for its antimicrobial properties.

Recently, Leung et al discovered another potential mechanism of action for dilute hypochlorite baths [9]. HOCl functions as an oxidant and can disrupt cellular signaling processes by oxidizing certain mediators [24]. Nuclear factor-κB (NF-κB) is a protein complex that plays a central role in many different processes, including inflammation, aging, skin development, and radiation response [24]. Radiation injury activates NF-κB, which drives the cellular responses that can ultimately lead to radiation dermatitis [25, 26]. NF-κB plays a role in normal skin homeostasis as well [12-17]. NF-κB is also influenced by intracellular reduction-oxidation (redox) conditions [27]. NF-κB's role in skin homeostasis and radiation injury suggests that it will be an attractive target for the treatment of radiation dermatitis. Because NF-κB is a master regulator of inflammation, we hypothesize that dilute hypochlorite baths may function as an anti-inflammatory agent by modulating NF-κB signaling and inflammatory responses in the skin [24].

Leung et al found that HOCl inhibits intracellular NF-κB signaling by oxidizing an upstream regulator without impairing global gene transcription and protein signaling. In the skin of mice, a single brief exposure to topical HOCl significantly blocked NF-κB signaling. An established mouse model of radiation dermatitis was then used to assess whether hypochlorite could ameliorate acute radiation dermatitis. Radiation dermatitis was reproducibly induced on the backs of 4-week-old C57BL/6 female mice with 6 Gy irradiation for 10 days. Mice were randomized to receive a 30-minute bath in water (control) or dilute HOCl prior to each exposure to ionizing irradiation. Skin was examined daily and assessed using Radiation Therapy Oncology Group (RTOG) criteria, which grades skin ulceration as the highest score (grade 4). Skin ulceration is defined as round excavations that result in the complete loss of epidermis and some portion of the dermis. Compared to the control group, HOCl treated animals had a significantly lower RTOG score with scores of 1.8 ± 0.24 and 4.0 ± 0 with and without HOCl treatment, respectively, by day 30. While all control animals developed skin ulceration by day 20, none of the HOCl-treated animals developed skin ulceration even by day 30. Histological analysis of skin biopsies taken on day 14 revealed that the skin of irradiated control animals exhibited classical signs of radiation dermatitis, including a lichenoid infiltrate, loss of skin appendages, and epidermal/dermal swelling. In contrast, the skin of HOCl-treated animals was largely normal, with retention of skin appendages and a mild increase in dermal cellularity. Finally, irradiation of mice skin induced the expression of five well-established NF-κB–dependent genes, and HOCl exposure significantly diminished this response. From clinical, histological, and molecular perspectives, it appeared that dilute bleach baths attenuated acute radiation dermatitis in mice.

HOCl is a safe, well-characterized, inexpensive, and widely available topical agent. The rationale for the starting regimen of this study is based on the methods from the prior mouse work and prior published human studies. At dilute concentrations, hypochlorite is safe for human skin contact as demonstrated in a prior clinical trial using the same concentration [18]. Hypochlorite is stable under normal use and storage conditions [28]. It is a strong oxidizing agent and does react with household chemicals such as toilet bowl cleaners, rust removers, vinegar, acids, and ammonia containing products

to produce hazardous gases, such as chlorine and other chlorinated species [28]. Encounters with such products is not planned nor anticipated for this study.

2.3 Study Design

This is a single-institution, randomized, double-blind, placebo-controlled clinical trial to investigate the role of topical HOCl in preventing radiation dermatitis in patients undergoing radiation therapy for head and neck cancer.

Patients will be screened at the time of radiation oncology consultation. If eligible, patients will be offered participation and consented for enrollment. Per standard of care, simulation for radiation treatment and the treatment planning process will be performed over two weeks. Patients can be consented prior to or within 3 days following the start of radiation treatment. After consent, a baseline clinical skin assessment will be performed, and patients will be stratified by type of chemotherapy (cisplatin, cetuximab, or none) randomized to the control arm or the experimental arm. Randomization will be performed by the study coordinator and will not be disclosed to the patient or the treating physician. The experimental arm will apply daily topical dilute HOCl for 10 minutes within 3 hours prior to radiation treatment. The control arm will apply daily topical placebo (water) for 10 minutes within 3 hours prior to radiation treatment. Clinical skin assessments will be performed by the treating physician once weekly during the radiation treatment course per standard of care, and radiation dermatitis will be graded according to both the Stanford Radiation Dermatitis Scoring System and the CTCAE v4.03 Scoring System. On both study arms, when the patient develops Grade E radiation dermatitis per the Stanford Radiation Dermatitis Scoring System, defined as moist desquamation within the radiation treatment field, requiring treatment (not prophylaxis) with topical dilute HOCl, the patient will have met the endpoint of the study, and the patient will be switched to standard-of-care treatment for radiation dermatitis consisting of topical dilute HOCl applied daily. For patients who do not develop Grade E radiation dermatitis during the radiation treatment course, a final skin assessment will be performed +/- 10 days after the last day of radiation treatment. Photos of skin within the radiation treatment field will be taken at the time of each clinical assessment. In addition, enrolled patients will complete the Modified Brief Pain Inventory questionnaire at the time of randomization, at 40-50 Gy of radiation treatment, on the last day of the radiation treatment course +/- 10 days, and at the follow-up visit 3-12 weeks after the completion of the radiation treatment course.

There is currently no external sponsorship or funding for this protocol.

2.3.1 Modified Brief Pain Inventory

Patients with moderate-severe radiation dermatitis often experience significant pain and discomfort until the skin heals, which can sometimes take up to 2-3 weeks. In order to assess patient reported levels of pain, patients will be asked to complete the Modified Brief Pain Inventory (MBPI) at the time of randomization, at 40-50 Gy of treatment, on the last day of radiation treatment +/- 10 days, and at the first follow-up visit 3-12 weeks after completion of the radiation treatment course. The MBPI allows patients to rate the severity of their pain as well as the degree to which their pain interferes with normal activities. There are seven pain severity items and seven pain interference items rated on a 0-10 Likert scale. It will take approximately 5 minutes to complete (ref; Appendix D).

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix A.

3.1 Inclusion Criteria

3.1.1 Patients with head and neck cancer who plan to undergo radiation therapy to the head and neck region

3.1.2 Patients must be at least 18 years of age

3.1.3 Patients must be able to understand and the willingness to sign a written informed consent document. A patient can be consented prior to or within 3 days following the start of radiation treatment.

3.2 Exclusion Criteria

3.2.1 Prior external beam radiation therapy (EBT) to the head and neck region or prior chemotherapy for head and neck cancer (induction chemotherapy and I-131 treatment NOT excluded)c

3.2.2 Patients whose physician-approved radiation treatment plan indicates a maximum prescription dose of less than 45 Gy

3.2.3 Patients with scleroderma or discoid lupus

3.3 Informed Consent Process

All participants will be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants will be required to sign the IRB approved informed consent prior to participation in any study specific procedure. The participant will receive a copy of the signed and dated consent document. The original signed copy of the consent document will be retained in the medical record or research file.

4. TREATMENT PLAN

4.1 Description of Treatment Plan

Patients will be screened for study eligibility by the research team when they arrive for their initial consultation for radiotherapy. If eligible and willing to participate, patients will sign informed consent and be enrolled in the study.

Baseline

Patients will undergo a clinical skin assessment by the treating physician. Patients will also complete the MBPI, and photographs will be taken of the neck to represent their baseline skin. Patients will be stratified by type of chemotherapy and randomized.

During Radiation Therapy

Prior to each radiation treatment, the study agent or placebo (depending on randomization arm) will be applied to the area of the skin to be irradiated for 10 minutes within 3 hours of the patient's daily scheduled radiotherapy treatment. A nurse or qualified research member will instruct the patient on its application on the day of trial consent. After this initial instruction, the patient will self-apply the solution to their skin prior to treatment when he/she arrives to the radiation treatment area. There are clinic rooms that the patient can utilize to self-apply the solution prior to their daily radiation treatment. A nurse or qualified research member will check in with the patient once per week and

answer any questions if applicable. Patients will be instructed to use Vaseline as a moisturizer during the radiation treatment course per standard of care.

A clinical skin assessment by the treating physician will be performed once weekly during the radiation treatment course and at the end of radiation treatment +/- 10 days. At each clinical skin assessment, skin toxicity will be graded using the Stanford Radiation Dermatitis Scoring System and the CTCAE Scoring System. Photographs will also be taken at 40-50 Gy of radiation treatment and at the end of radiation treatment +/- 10 days.

Patients will also complete the Modified Brief Pain Inventory at the time of randomization, at 40-50 Gy of radiation treatment, at the end of radiation treatment +/- 10 days, and at the follow-up visit 3-12 weeks after the completion of the radiation treatment course.

Follow Up

During the patient's follow up appointment 3-12 weeks after completion of the radiation treatment course, the patient will complete the MBPI, a clinical skin assessment will be performed, and photographs will be taken of their treatment area.

4.2 General Concomitant Medication and Supportive Care Guidelines

There are no concerns for concomitant medications or additional treatments. Patients will undergo standard of care radiation therapy and the risks and guidelines will be appropriately discussed and outlined in person with the treating physician, in addition to the informed consent. Patients will continue standard skin care as recommended by their treating physician.

4.3 Criteria for Removal from Study

Patients will be removed from the study if the patient experiences a severe allergic reaction in the treatment area and/or there is a significant worsening of dermatitis according to clinical assessment at the patient's current radiotherapy dose. If the patient is removed from the study, they will no longer receive the study agent concurrently with their radiotherapy, however, they may continue to undergo radiotherapy per standard of care and clinical assessment.

4.4 Alternatives

This study is optional. The alternative is to not participate in the study and receive standard radiation therapy without the study treatment.

5. STUDY AGENT INFORMATION

5.1 Study Agent

The study agent is hypochlorite (HOCl) at a concentration of 0.0051%, otherwise known as modified Dakin's solution. Clorox bleach will be diluted to attain this concentration.

5.2 Availability

The dilute HOCl solution will be provided to the patient.

5.3 Agent Accountability

The dilute HOCl solution will be stored in a locked cabinet in the Cancer Center.

6. DOSE MODIFICATIONS

There will be no dose modifications during this study. Patients will be removed from the study if they experience a significant worsening of dermatitis according to clinical assessment at the patient's current radiotherapy dose. The study agent will be discontinued and they will continue with radiotherapy alone and standard of care management for radiation dermatitis.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

Potential risks associated with dilute HOCl are skin itching and skin irritation. Prior human clinical trials demonstrated no significant risk of dilute 0.005% hypochlorite. One patient had itching and mild skin irritation. Because we are diluting the hypochlorite, we do not have significant concern for using concentrations that are too high.

7.2 Adverse Event Reporting

Adverse events will be graded according to CTCAE v4.03 and Stanford Radiation Dermatitis Scoring System. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director (PD) or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Informed Consent, Protocol Document, or Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution, or until 30 after the last dose of the study treatment.

Skin-related SAEs CTCAE Grade 4 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of 'Unanticipated Problem' will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences.

8. CORRELATIVE STUDIES

There will be no correlative studies involved in this investigation.

9. STUDY CALENDAR

	Baseline prior to Radiation Treatment	During Radiation Treatment	Follow-Up (3-12 weeks)
Randomization	X		
Blinded Solution Application (HOCl vs placebo)		X[A]	
HOCl Treatment		X[B]	
Clinical Skin Assessment	X	X[C]	X
QOL/Pain Questionnaire	X	X[D, E]	X
Photos of Neck	X	X[D, E]	X

A: Applied each day for 10 minutes within 3 hours of radiation treatment
B: Starting at the onset of Grade E Radiation Dermatitis during radiation treatment, HOCl will be applied as treatment per standard of care for both study arms
C: Performed once weekly by the treating physician and on the last day of radiation treatment +/- 10 days
D: Administered at 40-50 Gy of radiation treatment
E: Administered on the last day of radiation treatment +/- 10 days

10. MEASUREMENTS

10.1 Assessment of Outcome

Patients will be assessed on a weekly basis during radiation treatment as per standard of care. At each weekly on-treatment visit, a clinical skin assessment (physical exam) will be performed and documented per standard of care.

In addition to standard management, all patients enrolled on this study will be required to have photos of the neck taken at four time points: at the time of randomization, at 40-50 Gy of radiation treatment, at the end of radiation treatment +/- 10 days, and at the follow-up visit 3-12 weeks after completion of radiation treatment. To ensure consistency, photos will be taken with standardized equipment.

10.2 Inter-Rater Reliability

Patients enrolled on this study will be treated by experienced radiation oncologists. Inter-rater reliability will be established by a run-in training session. Prior to opening the study for accrual, these physicians will undergo a training session for the grading of radiation dermatitis. The training session will involve the physicians' review of 10 photos of the neck of patients undergoing treatment for head and neck cancer at various time points during treatment. Physicians will be blinded to the time point of the photo but will have access to the documented skin exam at the time the photo was taken. Each physician will assign a grade of radiation dermatitis for each photo, and the results will be assessed for reliability between the physicians with kappa statistics. A target kappa statistic of 0.8 will define good inter-rater reliability. If the target kappa statistic after the first set of photos is not met, the physicians will discuss and come to a consensus for each photo. A second set of 10 photos will then be assessed individually, and the kappa statistic will be again calculated. This process will be repeated for three iterations or until the target kappa score of 0.8 is met, whichever comes first.

If the kappa statistic of 0.8 is not met, a jurisdiction will be held every three months during the accrual of the trial. The jurisdiction will involve both physicians reviewing every photo of every patient enrolled since the previous jurisdiction (or start of the trial in case of the first jurisdiction). For the photos on which there is disagreement, the physicians will meet to discuss and come to a consensus grade for each photo. The consensus grade will be recorded as the final grade for that photo.

If the target kappa statistic of 0.8 is met and good inter-rater reliability is established, then spot-checks will be performed every three months during the accrual of the trial. A spot-check will involve the physicians assessing a set of the same 5 randomly-selected photos.

10.3 Primary Outcome

The primary outcome is the proportion of patients who experience Grade E radiation dermatitis as defined by the Stanford Radiation Dermatitis Scoring System in each arm of the study.

10.3.1 Measurement Methods

The primary outcome will be assessed and graded by the treating physician, a radiation oncologist, who will give an individual score of the irradiated area at baseline, once weekly during radiation treatment course, at the end of the radiation treatment course +/- 10 days, and at the patient's follow up visit 3-12 weeks after completion of the radiation treatment course. The final grading of radiation dermatitis for each time point will be subject to the inter-rater reliability processes described in Section 10.2.

10.4 Secondary Outcomes

The secondary outcomes are to assess the time to development of Grade E radiation dermatitis and the quality of life and level of pain before, during, and after radiotherapy.

10.4.1 Measurement Methods

Patients will be seen once weekly during radiation therapy by the treating physician, who will perform the weekly clinical skin assessments. At the time Grade E radiation dermatitis develops, the study coordinator will be notified, and the patient will be switched to standard management for radiation dermatitis.

The MBPI will be administered at the time of randomization, at 40-50 Gy of radiation treatment, at the end of radiation treatment +/- 10 days, and at the follow-up visit 3-12 weeks after completion of radiation treatment.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

12. STATISTICAL CONSIDERATIONS

12.1 Randomization Method

Block randomization will be used to stratify by type of chemotherapy: cisplatin, cetuximab, no chemotherapy.

12.2 Sample Size Justification

The primary endpoint is the proportion of patients who develop Grade E radiation dermatitis (as defined by the Stanford Radiation Dermatitis Scoring System) in each arm during a course of radiation therapy. From prior clinical experience, we anticipate that 80% of patients will experience Grade E radiation dermatitis with standard skin care. In order to detect a 20% reduction in patients with Grade E radiation dermatitis (80% vs 60% in those treated with dilute hypochlorite solution) with Type I error of 0.05 and Type II error of 20% (power of 80%), 170 patients will be enrolled.

12.3 Primary Analysis

The primary endpoint is the proportion of patients who develop Grade E radiation dermatitis (as defined by the Stanford Radiation Dermatitis Scoring System) in each arm during a course of radiation therapy. A multiple logistic regression model will be used controlling for type of chemotherapy (cisplatin, cetuximab, none).

12.4 Secondary Analyses

Secondary endpoints include the time to development of Grade E radiation dermatitis and the quality-of-life and pain scores in each arm. Time to development of radiation dermatitis will be defined as time from Day 1 of radiation treatment to the first appearance of Grade E radiation dermatitis. This data will be summarized with Kaplan-Meier curves. A Cox proportional hazards model will be used to compare the treatment groups. The model will adjust for type of chemotherapy and other patient characteristics should they prove to be significant. A repeated measures model will be used to analyze the quality-of-life and pain scores. The model will adjust for type of chemotherapy and other patient characteristics should they prove to be significant.

12.5 Accrual Estimates

We estimate that approximately 2 patients with head and neck cancer start radiation therapy in a given week in our department. Assuming that 2/3 of these patients would be eligible for this study and would provide consent with a 10% attrition rate, we estimate that this study will complete accrual of 170 patients in 142 weeks (or 36 months).

12.6 Inter-Rater Reliability Testing

Inter-rater reliability will be evaluated using the kappa statistic. A kappa statistic of 0.8 will define good inter-rater reliability. For details of how this method will be implemented, see Section 10.2.

12.7 Criteria for Future Studies

If our hypothesis is correct and the hypochlorite solution reduces the incidence of Grade E radiation dermatitis, we plan to initiate a multi-institution, phase III randomized clinical trial with the intention of establishing the prophylactic use of topical dilute hypochlorite solution as standard of care to prevent radiation dermatitis in patients undergoing radiation therapy for head and neck cancer.

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APPENDICES

APPENDIX A**: Participant Eligibility Checklist**

A Participant Eligibility Checklist must be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist must be retained in the patient's study file and the study's Regulatory Binder.

The study coordinator, treating physician and an independent reviewer must verify that the participant's eligibility is accurate, complete, and legible in source records. A description of the eligibility verification process should be included in the EPIC or other Electronic Medical Record progress note.

Protocol Title:	
Protocol Number:	
Principal Investigator:	**Dr. Beth Beadle**

II. Subject Information:

Subject Name/ID:
Gender: ☐ Male ☐ Female

III. Study Information:

SRC Approved ☐ IRB Approved ☐ Contract signed ☐

IV. Inclusion/Exclusion Criteria

Inclusion Criteria (From IRB approved protocol)	**Yes**	**No**	**Supporting Documentation***
1. Patients with head and neck cancer who plan to undergo radiation therapy to the head and neck region	☐	☐	
2. Patient must be at least 18 years of age	☐	☐	
3. Ability to understand and the willingness to sign a written informed consent document	☐	☐	
Exclusion Criteria (From IRB approved protocol)			
1. Prior radiation therapy to the head and neck region or prior chemotherapy for head and neck cancer (induction chemotherapy NOT excluded)	☐	☐	
2. Maximum RX dose <45 Gy in the approved radiation treatment plan	☐	☐	
3. Patients with scleroderma or discoid lupus	☐	☐	

*All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

IV. Statement of Eligibility

By signing this form of this trial I verify that this subject is [☐ **eligible** / ☐ **ineligible**] for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Physician Signature:	Date:
Printed Name:	

Secondary Reviewer Signature:	Date:
Printed Name:	

Study Coordinator Signature:	Date:
Printed Name:	

APPENDIX B: **Stanford Radiation Dermatitis Scoring System**

Grade	Clinical finding
A	**No skin change**
B	**Faint, barely detectable erythema**
C	**Follicular rash, hyperpigmentation, evolving erythema**
D	**Dry desquamation, brisk erythema**
E	**Moist desquamation**
F	**Bleeding, ulceration, and/or infection**

APPENDIX C: CTCAE Version 4.03

Grade	Clinical finding
0	No skin change
1	Faint erythema or dry desquamation
2	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
3	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion
4	Life-threatening consequences; skin necrosis or ulceration of full-thickness dermis; spontaneous bleeding from involved site; skin graft indicated
5	Death

APPENDIX C: Modified Brief Pain Inventory

Please fill in the following:
First Name (1)
Last Name (2)

Time point for survey:
- ❍ Baseline prior to radiation treatment (1)
- ❍ 40-50 Gy of radiation treatment (2)
- ❍ Last day of radiation treatment (3)
- ❍ Follow-up visit 3-12 weeks after radiation treatment course (4)

Q1 Please rate your current level of skin discomfort.
- ❍ 0 (0)
- ❍ 1 (1)
- ❍ 2 (2)
- ❍ 3 (3)
- ❍ 4 (4)
- ❍ 5 (5)
- ❍ 6 (6)
- ❍ 7 (7)
- ❍ 8 (8)
- ❍ 9 (9)
- ❍ 10 (10)

Q2 Please rate your pain by selecting the one number that best describes your pain at its worst in the last 24 hours.
- ❍ 0 (0)
- ❍ 1 (1)
- ❍ 2 (2)
- ❍ 3 (3)
- ❍ 4 (4)
- ❍ 5 (5)
- ❍ 6 (6)
- ❍ 7 (7)
- ❍ 8 (8)
- ❍ 9 (9)
- ❍ 10 (10)

Q3 Please rate your pain by selecting the one number that best describes your pain at its least in the last

24 hours.

- ❍ 0 (0)
- ❍ 1 (1)
- ❍ 2 (2)
- ❍ 3 (3)
- ❍ 4 (4)
- ❍ 5 (5)
- ❍ 6 (6)
- ❍ 7 (7)
- ❍ 8 (8)
- ❍ 9 (9)
- ❍ 10 (10)

Q4 Please rate your pain by selecting the one number that best describes your pain on the average.

- ❍ 0 (0)
- ❍ 1 (1)
- ❍ 2 (2)
- ❍ 3 (3)
- ❍ 4 (4)
- ❍ 5 (5)
- ❍ 6 (6)
- ❍ 7 (7)
- ❍ 8 (8)
- ❍ 9 (9)
- ❍ 10 (10)

Q5 Please rate your pain by selecting the one number that tells how much pain you have right now.

- ❍ 0 (0)
- ❍ 1 (1)
- ❍ 2 (2)
- ❍ 3 (3)
- ❍ 4 (4)
- ❍ 5 (5)
- ❍ 6 (6)
- ❍ 7 (7)
- ❍ 8 (8)
- ❍ 9 (9)
- ❍ 10 (10)

Q6 What treatments or medication are you receiving for your pain?

Q7 In the last 24 hours, how much relief have pain treatments or medications provided? Please select

the one percentage that most shows how much relief you have received?

- ❍ 0% (No Relief) (0)
- ❍ 10% (1)
- ❍ 20% (2)
- ❍ 30% (3)
- ❍ 40% (4)
- ❍ 50% (5)
- ❍ 60% (6)
- ❍ 70% (7)
- ❍ 80% (8)
- ❍ 90% (9)
- ❍ 100% (Complete Relief) (10)

Select the one number that describes how, during the past 24 hours, pain has interfered with your:

Q8 General Activity

- ❍ 0 (0)
- ❍ 1 (1)
- ❍ 2 (2)
- ❍ 3 (3)
- ❍ 4 (4)
- ❍ 5 (5)
- ❍ 6 (6)
- ❍ 7 (7)
- ❍ 8 (8)
- ❍ 9 (9)
- ❍ 10 (10)

Q9 Mood

- ❍ 0 (0)
- ❍ 1 (1)
- ❍ 2 (2)
- ❍ 3 (3)
- ❍ 4 (4)
- ❍ 5 (5)
- ❍ 6 (6)
- ❍ 7 (7)
- ❍ 8 (8)
- ❍ 9 (9)
- ❍ 10 (10)

Q10 Walking Ability

- ❍ 0 (0)
- ❍ 1 (1)
- ❍ 2 (2)
- ❍ 3 (3)
- ❍ 4 (4)
- ❍ 5 (5)
- ❍ 6 (6)
- ❍ 7 (7)
- ❍ 8 (8)
- ❍ 9 (9)
- ❍ 10 (10)

Q11 Normal Work (includes both work outside the home and housework)

- ❍ 0 (0)
- ❍ 1 (1)
- ❍ 2 (2)
- ❍ 3 (3)
- ❍ 4 (4)
- ❍ 5 (5)
- ❍ 6 (6)
- ❍ 7 (7)
- ❍ 8 (8)
- ❍ 9 (9)
- ❍ 10 (10)

Q12 Relations with other people

- ❍ 0 (0)
- ❍ 1 (1)
- ❍ 2 (2)
- ❍ 3 (3)
- ❍ 4 (4)
- ❍ 5 (5)
- ❍ 6 (6)
- ❍ 7 (7)
- ❍ 8 (8)
- ❍ 9 (9)
- ❍ 10 (10)

Q13 Sleep

- ❍ 0 (0)
- ❍ 1 (1)
- ❍ 2 (2)
- ❍ 3 (3)
- ❍ 4 (4)
- ❍ 5 (5)
- ❍ 6 (6)
- ❍ 7 (7)
- ❍ 8 (8)
- ❍ 9 (9)
- ❍ 10 (10)

Q14 Enjoyment of Life

- ❍ 0 (0)
- ❍ 1 (1)
- ❍ 2 (2)
- ❍ 3 (3)
- ❍ 4 (4)
- ❍ 5 (5)
- ❍ 6 (6)
- ❍ 7 (7)
- ❍ 8 (8)
- ❍ 9 (9)
- ❍ 10 (10)

Q15 At this point, how much do you feel that this skin treatment will improve or prevent your skin discomfort during radiation treatment? **(Asked only at baseline**)

- ❍ 0% (No Relief) (0)
- ❍ 10% (1)
- ❍ 20% (2)
- ❍ 30% (3)
- ❍ 40% (4)
- ❍ 50% (5)
- ❍ 60% (6)
- ❍ 70% (7)
- ❍ 80% (8)
- ❍ 90% (9)
- ❍ 100% (Complete Relief) (10)