Protocol

Topical Esomeprazole for the Prevention and Treatment of Radiation Dermatitis in Patients With Head and Neck Cancer: Protocol for a Phase 2 Randomized Controlled Trial

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Abstract

Background: Radiation dermatitis (RD) is a common and clinically significant toxicity affecting the majority of patients undergoing external beam radiation therapy, particularly those treated for head and neck cancer (HNC). RD can impair quality of life, limit treatment intensity, and compromise oncologic outcomes; yet, there is no established standard-of-care for its prevention or management. Preclinical studies suggest that a topically reformulated proton pump inhibitor (PPI), esomeprazole (Dermaprazole), has antioxidant, anti-inflammatory, and antifibrotic properties that may mitigate radiation-induced skin injury.

Objective: This phase 2 randomized controlled trial aims to evaluate the potential safety, feasibility, and efficacy of prophylactic topical Dermaprazole compared with standard supportive care (Aquaphor) in reducing the incidence and severity of clinically significant RD in patients with HNC receiving definitive chemoradiation.

Methods: This is a prospective, single-center, randomized controlled trial with a 2:1 allocation ratio. A total of 45 adults (≥18 y) with biopsy-confirmed head and neck malignancy planned to receive definitive chemoradiation of at least 66 Gy will be enrolled. Participants will be randomized to receive twice-daily topical Dermaprazole or Aquaphor beginning at computed tomography (CT) simulation and continuing through 2 weeks after completion of radiation therapy. The primary outcome is the rate and severity of RD, assessed weekly during treatment using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5 by the treating radiation oncologist, with blinded dermatologic assessment based on standardized medical photography. Feasibility outcomes include accrual rate, treatment compliance, and questionnaire completion rates. Secondary outcomes include time to onset and healing of grade ≥2 RD, quality of life assessed using the Skindex-16 instrument, radiation dose thresholds associated with dermatitis, and changes in inflammatory biomarkers (C-reactive protein, tumor necrosis factor-α, interleukin [IL]-1β, and IL-6). More specifically, secondary outcomes will be assessed through serial CTCAE version 5 evaluations for onset and healing, Skindex16 questionnaires for quality of life, radiation dose-volume parameters for dermatitis thresholds, and serum inflammatory marker concentration measurements before, during, and after treatment.

Results: The study began in June 2022 and has completed enrollment. Data analysis will commence following completion of data collection, with results expected to be published by 2027.

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Conclusions: Should Dermaprazole demonstrate efficacy in reducing RD in patients undergoing radiation therapy, it may offer an alternative or adjunctive treatment option for the prevention and management of RD, potentially reducing treatment-related morbidity and improving patients' quality of life during radiotherapy.

Trial Registration: ClinicalTrials.gov NCT04865731; https://clinicaltrials.gov/study/NCT04865731

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KEYWORDS

radiation dermatitis; oncology; drug repurposing; radiodermatitis; esomeprazole; administration; topical; head and neck neoplasms; proton pump inhibitors

Introduction

Background

Radiation dermatitis (RD) is one of the most common side effects seen following radiation treatment of cancer, affecting more than 90% of patients receiving external beam ionizing radiation [1]. Patients undergoing radiotherapy often experience several cutaneous symptoms such as dry and wet desquamation, skin necrosis, ulcers, radiation-induced keratosis, telangiectasias, scleroderma, and skin cancer, which lead to increased morbidity and impaired quality of life [2]. There is no standard of care treatment for RD; topical corticosteroids can be used but are associated with unpleasant side effects such as epidermal thinning, erythema, telangiectasia, and purpura [3]. In some severe cases, the side effects of both RD and corticosteroids can limit the duration and intensity of treatment, consequently compromising the patient's treatment plan [4]. There is a clear and urgent demand for the development of a safe and effective treatment option for those at risk of developing RD as well as those already affected.

RD is a broad spectrum of symptoms and manifestations of postirradiation skin toxicity [5]. According to the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) and the Radiation Therapy Oncology Group (RTOG) scoring systems (Table 1), mild dermatitis (grade 1) is characterized by mild redness (erythema), epidermal thickening (hyperkeratosis), or dry desquamation and appears shortly after treatment initiation [6,7]. Moderate dermatitis (grade 2) occurs within 2 weeks of radiotherapy and manifests as painful and intense erythema, loss of hair from the root (epilation), blisters, and edema. Of note, the presence of grade 2 toxicity is generally regarded as clinically significant toxicity. In severe dermatitis (grades 3 and 4), moist desquamation occurs excessively and may lead to persistent inflammation, full-thickness skin necrosis, and severely painful ulceration that is prone to infection. The acute effects occur almost immediately at radiation doses between 2 and 40 Gray (2-40 Gy), whereas chronic effects occur several months to years after exposure to high radiation doses (>45 Gy), and typical skin changes include atrophy, scarring, and spider veins (telangiectasia) [8].

Table 1. Common Terminology Criteria for Adverse Events (CTCAE) grading criteria for radiation dermatitis.

Grade	Injury, poisoning, and procedural complications
Grade 1	Faint erythema or dry desquamation
Grade 2	Moderate to brisk; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema
Grade 3	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion
Grade 4	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated
Grade 5	Death

The effect of radiation on the skin is in part due to its effect in promoting the production of highly reactive free radicals that are involved in DNA damage [9]. In addition, radiation upregulates several inflammatory cytokines (eg, tumor necrosis factor [TNF]-α, interleukin [IL]-1β, IL-6, vascular cell adhesion molecule 1 [VCAM-1], and intercellular adhesion molecule 1 [ICAM-1]) that can exacerbate sustained injury and compromise skin integrity [10]. For example, almost all patients with head and neck cancer (HNC) are profoundly affected by severe dermatitis (grade 2 or higher) due to the development of serious inflammatory skin reactions described above [11]. Additionally, acute RD is the most common acute response after adjuvant radiotherapy in patients with breast cancer due to the innate inflammatory response [12]. Therefore, treatments aimed at the radiation-induced inflammatory process may effectively relieve the symptoms in patients with RD.

Several nonpharmacological and pharmacological approaches have been evaluated for the prevention, treatment, or management of severe RD; however, the use of many of these agents is not recommended either due to lack of efficacy or insufficient clinical data [13]. Meanwhile, various pharmacological agents have been developed to mitigate RD. Of these, topical corticosteroids are the archetype. Among the steroid-based products, mometasone furoate (0.1%), betamethasone (0.1%), and hydrocortisone (1%) are extensively studied in clinical trials [14]. While steroid use has been shown in clinical trials to decrease RD, some drawbacks have limited their widespread use, including concern regarding risk of

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cutaneous atrophy, stretch marks (striae), and secondary skin infection (eg, cellulitis and candidiasis) [15].

Proton pump inhibitors (PPIs) now have well-described anti-inflammatory effects [16]. Interestingly, earlier research discovered that PPIs directly regulate the nitric oxide synthase (NOS) pathway via inhibition of the inducible isoform (inducible nitric oxide synthase [iNOS]), which is significantly expressed in skin cells in response to inflammatory stimuli as in radiation or chemotherapy [17-19]. The nitric oxide (NO) catalyzed by iNOS is short-lived and rapidly oxidizes to peroxynitrite (OONO-), a highly reactive molecule that is involved in the generation of nitrotyrosine, a more stable product that is involved in tissue inflammation [20]. Additionally, a number of inflammatory cytokines released during chemoradiation are known to enhance NO production [21]. It has been shown that regulation of the iNOS pathway by PPIs is due to their direct interaction with dimethylarginine dimethylaminohydrolase (DDAH), an enzyme that breaks down asymmetric dimethylarginine (ADMA, the endogenous and competitive NOS inhibitor) [20]. Subsequently, esomeprazole was discovered to be the most potent PPI that controls the proinflammatory enzyme DDAH and many classic proinflammatory cytokines (eg, nuclear factor kappa B [**NF-κB**], TNF-α, IL-1β, IL-6, VCAM-1, and ICAM-1) that are reported to be pathologically upregulated in RD [20].

A recent study reformulated esomeprazole into a Lipoderm-based cream (Dermaprazole) that retained the inherent biologic antioxidant, anti-inflammatory, and antifibrotic effects with the goal of evaluating its efficacy as a RD drug in a mouse model [20]. Remarkably, their study showed that while 90% of the animals in a corticosteroid control group had grade 2 or higher dermatitis, Dermaprazole mitigated the RD in most of the animals, with only 20% showing grade 2 or higher RD. They also observed that Dermaprazole use led to significantly lower ulceration, necrosis, inflammation, and fibrosis, with most treated animals showing complete or nearly complete wound closure within 4 weeks following exposure to ionizing radiation. The current protocol aims to determine the effectiveness and safety of the topically reformulated PPI, Dermaprazole, in relieving RD in patients with definitive HNC.

Objectives

The main focus of this phase 2 clinical trial is to determine if objectively lower rates of significant RD occur with prophylactic Dermaprazole for patients with HNC receiving definitive radiation when compared with patients receiving Aquaphor. More specifically, the study will measure the rate of clinically significant (CTCAE version 5 grade 2 or higher) RD observed in patients receiving the topically reformulated PPI and compare it with the patients receiving Aquaphor alone. The primary endpoint is the between-group difference in the proportion of patients who develop clinically significant RD during treatment. This measure will be reported weekly during treatment by the treating radiation oncologist and blindly reviewed by a board-certified dermatologist via medical photography post treatment. Unblinding may be done by the primary investigator if deemed necessary.

Methods

Trial Design

This trial uses a 2:1 randomized study design using a computer-generated randomization sequence. The allocation sequence will be generated before enrollment and maintained by study personnel not involved in clinical outcome assessment. A 2:1 allocation favoring Dermaprazole was chosen to increase experience with its safety and tolerability while maintaining an appropriate control group for comparison. In this study, enrolled patients will be treated with the active reformulated PPI or with Aquaphor alone followed by radiation therapy (refer to the study flow diagram). Patients will also be followed for long-term follow-up and assessment post treatment. Long-term follow-up will assess chronic radiation-associated cutaneous toxicities including fibrosis, telangiectasia, pigmentary changes, and other delayed skin changes.

Study Setting

This is a single-center study taking place in the Mays Cancer Center of the University of Texas (UT) Health Science Center at San Antonio. This study has been authorized by the UT Health Institutional Review Board (IRB). In addition, it is registered with the National Institutes of Health's US National Library of Medicine database, ClinicalTrials.gov (NCT04865731).

Eligibility Criteria

Patients will have to fulfill all the inclusion criteria, and they will be excluded from this study if they fulfill any of the exclusion criteria (Textbox 1).

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patients with head and neck malignancy (including radiation therapy to head and neck cancers of any histology and/or neck lymphatics, excluding brain malignancies)
- Biopsy-proven diagnosis of head and neck malignancy
- Planned to receive definitive chemoradiation of at least 66 Gy
- Age 18 years or older
- Eastern Cooperative Oncology Group performance status 0-2
- Written informed consent
- History and physical within 12 weeks of enrollment

Exclusion criteria

- Prior history of head and neck radiotherapy
- Neoadjuvant chemotherapy
- Any serious medical condition or illness that would preclude the safe administration of the trial treatment including, but not limited to, active infection, symptomatic heart failure, unstable angina, psychiatric illness, or social situation that would limit compliance with treatment
- Currently taking proton pump inhibitors. Patient remailed eligible if they discontinue the drug with physician approval
- Lack of concurrent chemotherapy
- Open wound at time of simulation
- Known autoimmune, connective tissue, or other skin disorder; or other theoretical radiosensitivity to include bullous pemphigoid, dermatomyositis, lupus of the skin, and scleroderma
- Pregnancy or lactating patients

Intervention

Definitive head and neck radiation treatment will follow standard practice. Variations (dose adjustments, delays, etc) that follow standard clinical practice are allowed and are not considered deviations, although these will be recorded to assess for interference.

Patients will be managed with twice-daily prophylactic use of the proposed intervention (Dermaprazole) topical cream for RD or Aquaphor. The amount of cream or Aquaphor will be 2cc per application and will be measured in prefilled capped syringes for every application.

The Dermaprazole topical cream will be manufactured by Village Pharmacy in Houston. After the product is compounded, it will be shipped overnight to the Mays Cancer Center Pharmacy in insulated shipping containers with temperature monitors. The cream will be stable for a minimum of 1 month in airtight containers under refrigerated conditions (2 ^{o}C-8 ^{o}C) and is stable at controlled room temperature for at least 1 week. Room temperature is 20 °C-25 °C (excursions permitted between 15 °C and 30 °C). A 1-week supply of the cream will be dispensed to the participant during study participation, with the exception that a 1.5- to 2-week supply will be provided at the time of computed tomography (CT) simulation (determined by the anticipated radiation start date) and a 2-week supply will be provided at the end of radiation treatment. A greater than 1-week supply may also be dispensed during holiday weeks (ie, Christmas week). The same method will be used for the dispensing of the Aquaphor except that refrigeration will not be done.

Patients will be instructed to apply the cream or Aquaphor along the area exposed to radiation from the day of simulation (ie, approximately 1 week prior to the start of radiation) to 2 weeks after completion, correlating with the acute phase of RD. In the event of a delay from the time of CT simulation to the start of radiation therapy, if the patient has no more than 3 days of interruption of the cream, this will not be considered a violation of the protocol. An interruption longer than 3 days will be considered a minor deviation. Patients who develop an open wound may be prescribed a topical antibiotic if indicated.

Neither the Dermaprazole cream nor the Aquaphor is expected to be irritating or sensitizing, but participants will be instructed to inform study personnel if a skin irritation occurs. If eye contact occurs, the participant will be instructed to flush the eyes with water while open and to inform study personnel. Additionally, compliance with intervention and use of other topical agents will be documented qualitatively during weekly assessments.

Outcomes

Primary Outcome Measures

First, the rates and severity of radiation-related toxicity will be defined using NCI CTCAE version 5 [22]. These will be used in the assessment by the treating radiation oncologist as well as during blinded review by the dermatologist. The following definitions will be used:

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- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Faint erythema or dry desquamation.
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self-care ADL. Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion.
- Grade 4: Life-threatening consequences; urgent intervention indicated. Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated.
- Grade 5: Death related to adverse event (AE).

Although not expected, if at half our expected enrollment, 50% or more of patients experience mild intervention-related toxicity, this treatment regimen will not be considered safe. The trial will be monitored for serious adverse events (SAEs) and stopped early for safety if 2 treatment-related grade 3 SAEs are reported or if 1 treatment-related grade 4-5 SAE is reported at any point of the trial.

Second, another primary end point will be feasibility, which is defined as the consideration of whether the protocol implementation will be successful in terms of accrual within the expected time frame, as well as whether patients would comply with the study protocol and necessary data collection is logistically feasible in the clinical setting. To evaluate feasibility, we will measure:

- Accrual rate and summary of causes for nonenrollment;
- Percentage of patients compliant with therapy, defined as receiving at least 66 Gy radiation to the head and neck while using prophylactic Dermaprazole as directed; and
- Compliance rate and rate of completion of the SkinDex16 forms.

All end points will be evaluated when the last patient completes their 3-month follow-up visit, although patients will continue with additional regular follow-up visits as described in the protocol schedule. Since, by that point, a patient would have completed all treatments, the data would provide an accurate estimate of compliance and acute toxicity.

For the study to be considered feasible, all of the following must be true:

1. No more than 5 patients fail to complete the treatment regimen.

2. No more than 15 participants fail to comply with prophylactic Dermaprazole cream application of at least once a day.

3. Enrollment takes no longer than 24 months.

4. Proportions of analyzable questionnaires at baseline, while on-treatment, and off-treatment during follow-up, and within questionnaires completion rates are no worse than 80%, 80%, and 60%, respectively.

Feasibility will be assessed separately using prescribed criteria related to accrual, treatment adherence, and completion of study assessments.

Secondary Outcome Measures

The following are the secondary outcome measures:

- Assess the highest grade of CTCAE version 5 RD during radiation treatment.
- Assess the time to occurrence of CTCAE version 5 grade 2 or higher acute RD.
- Assess the time to healing if CTCAE version 5 grade 2 or higher acute RD develops.
- To evaluate the quality of life via acute and long-term symptoms and symptom scores using the SkinDex16 scoring system.
- To evaluate the threshold dose at which RD appears in either arm, using skin dose tracking structures (V20 to V70 in 5 Gy increments reaching skin shell contours of “skin minus 3 millimeters” and “skin minus 5 millimeters”).
- To evaluate the threshold dose at which RD appears in either arm, using the same metrics as in 2.2.2.5, but with a new simulation scan in the last week of radiotherapy.
- To evaluate the effect of Dermaprazole on inflammatory markers—C-reactive protein (CRP), TNF-α, IL-1β, IL-6—by measuring values before, during, and after treatment. We expect this to give further evidence for the mechanism of action of Dermaprazole.

Toxicity will be reported as the frequency of each AE according to the CTCAE version 5.0, as well as the grade of each recorded AE. Generally, AEs in this system are graded from 1 to 5, with 1 corresponding to either mild or asymptomatic clinical manifestations of toxicity and 5 corresponding to death related to the AE. Clinically relevant toxicity will be defined as grade 2 or higher, while severe toxicity will be defined as grade 3 or higher. Acute toxicity will be defined as AEs that occur during or within 90 days after completing radiation therapy. Toxicities occurring more than 90 days after completion of radiation therapy will be classified as late or chronic toxicities and assessed during long-term follow-up. We will consider this intervention safe if there is a grade 1 toxicity rate of <50%, a grade 2 or higher toxicity rate of <10%, and no grade 3 or higher events.

Percentages of patients enrolled per month will be recorded. If the enrollment time exceeds 12 months, the study will be considered not feasible as written. Percentage of patients not enrolled will be summarized by cause.

Quality of life will be measured with the use of SkinDex16 questionnaires filled out by the patient at baseline, throughout treatment, at the completion of radiation treatment, and at each follow-up visit subsequently. The SkinDex16 is a validated 16-item patient-reported outcome measure that assesses the impact of skin disease on health-related quality of life across symptoms, emotions, and functioning [23]. We will also consider compliance to questionnaire completion and within questionnaires completion rates. This will be reported as the average proportion of questions within each form completed properly, without errors. As long as the rates are not below the

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minimum threshold defined above, the study will be considered feasible.

Participant Timeline

A summary of the study process is outlined in Table 2. The first screening visit will entail obtaining informed consent, review of inclusion and exclusion criteria, a comprehensive history and physical exam (within 12 weeks of registration), Eastern Cooperative Oncology Group (ECOG) performance status, pregnancy test (for women of child-bearing potential), SkinDex16 questionnaire, and a photographic documentation of the skin at baseline.

Standard-of-care will be followed according to the prescribing physician. Head and neck radiation of over 66Gy will be permitted with or without boost up to 70Gy (but not higher). Radiation is to be delivered 5 days per week (with exception of weeks with holidays), using intensity-modulated technique. CT-based simulation with thermoplastic mask and volumetric planning must precede treatment. Tissue-equivalent bolus is permitted on protocol. Daily cone beam CT images are required to confirm accurate delivery. Resimulation will be done in the last week of radiotherapy to allow for recalculation of beams.

Baseline, weekly on-treatment, and follow-up assessments will include a focused skin exam, ECOG performance status, AE or toxicity evaluation, including CTCAE version 5 evaluation of RD with note of components (erythema, epilation, fibrosis, etc), SkinDex16 questionnaire, photographic documentation of skin reaction with dermatologist's evaluation of CTCAE version 5 from this photography, compliance questionnaire (only while on treatment), and laboratory draws including CRP, TNF-α, IL-1β, and IL-6.

Patients will be followed for up to 60 months after completion of radiation or until death to assess intervention-related tolerance. The same measures will be recorded at the posttreatment follow-up except for the compliance questionnaire (Table 3). The month 1 visit will be defined as 30 (SD 14) days after completion of all radiation therapy. The month 3 visit will be defined as 90 (SD 28) days after completion of all radiation therapy. Long-term follow-up visits will occur at months 6, 9, 12, 18, 24, 36, 48, and 80 calculated from completion of all radiation therapy (SD 28 days).

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Table 2. Calendar of study assessments and testing.

Study procedures and assessments	Pretreatment	Head/Neck RT(Weekly)[a]									Posttreatment
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	
Screening											
Written informed consent	✓										
Inclusion and exclusion criteria	✓										
Physical											
Comprehensive history and physical	✓										
Focused skin exam (radiation oncologist)	✓	✓	✓	✓	✓	✓	✓	✓			
Medical photography[b]	✓	✓	✓	✓	✓	✓	✓	✓			
Assessments											
CTCAE[c] Version 5 Radiation Dermatitis (Radiation Oncologist)		✓	✓	✓	✓	✓	✓	✓			
CTCAE Version 5 Radiation Dermatitis (Blinded – Dermatologist)											✓
Adverse events or toxicity		✓	✓	✓	✓	✓	✓	✓			
SkinDex16 Questionnaire	✓	✓	✓	✓	✓	✓	✓	✓			
Treatment											
CT Simulation	✓							✓			
XRT[d]		✓	✓	✓	✓	✓	✓	✓			
Dermaprazole or Aquaphor[e]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Compliance Assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Laboratory draw											
Serum Pregnancy Test if Woman of Child-Bearing Potential	✓										
CRP[f], TNF-α[g], IL[h]-1β, IL-6	✓							✓[i]		✓	

[a]Weekly assessments to be performed within +/–3 days of the end of each week (defined by a period of 5 treatments).

[b]Photos will be taken with a Sony DSLR camera with 20.1 Megapixels. Photos will be uploaded to a protected research folder directly from the camera and the dermatologist will have access to the folder. The photos will be de-identified and labeled with study case number.

[c]CTCAE: Common Terminology Criteria for Adverse Events.

[d]XRT: radiation therapy.

[e]Refer to Intervention section for detailed instructions regarding Dermaprazole and Aquaphor.

[f]CRP: c-reactive protein.

[g]TNF: tumor necrosis factor.

[h]IL: interleukin.

[i]In the last week of radiotherapy, may be different than week 7.

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Table 3. Calendar of posttreatment assessment and long-term follow-up.

Study procedures and assessments	Posttreatment[a] assessment		Long-term follow-up (up to 60 months post-tx)	
	Month 1 (30 days posttreatment[b])	Month 3 (90 days posttreatment[c])	Every 3 months (M6, M9, M12[c])	Every year (M24, M36, M48, M60[c])
Physical				
Focused Skin Exam (Radiation Oncologist)	✓	✓	✓	✓
Medical Photography	✓	✓	✓	✓
Assessments				
CTCAE Version 5 Radiation Dermatitis (Radiation Oncologist)	✓	✓	✓	✓
CTCAE Version 5 Radiation Dermatitis (Blinded – Dermatologist)	✓	✓	✓	✓
Adverse Events/Toxicity	✓	✓	✓	✓
SkinDex16	✓	✓	✓	✓

[a]Timing of posttreatment visits is from the completion of radiotherapy.

[b]To be completed within +/– 14 days.

[c]To be completed within +/– 28 days.

Sample Size

Participants will continue to be enrolled and monitored for toxicity per the above criteria until 30 patients in arm 1 and 15 patients in arm 2 have completed the course of head and neck radiation as evaluable patients. Patients will be randomized by computer in a 2:1 fashion. Per our current database, the clinic is treating approximately 60 eligible patients per year. As such, accrual should take no longer than 12 months but will be allowed to extend to up to 24 months without closing the study.

Initial sample size for this study was estimated as if this study was conducted as a phase 2 study. Sample size calculation was determined using significance (α) of .05, to at least detect a difference in incidence of 45% and power (β) of 80%. In general, rates of clinically bothersome grade 2 dermatitis in the literature appear to be approximately 65% [24]. Based on our preclinical study with animal and human skin models, we expect 20% of the Dermaprazole arm to have CTCAE grade 2 or higher RD [20]. Given these values, we calculated our final sample size to be approximately 39 and we aim to enroll 45 participants.

Recruitment and Informed Consent

The 45 patients, female and male, with biopsy confirmed head and neck malignancy will be recruited from the Radiation Oncology clinic at Mays Cancer Center. Informed consent will be obtained by research staff that have completed the Collaborative Institutional Training Initiative (CITI) Good Clinical Practice (GCP) clinical research training certification. Also, the research study staff will be trained in both general clinical trial procedures and tasks specific to this study.

Data Collection, Management, and Confidentiality

Patient information will be acquired from patient medical records within the clinical site electronic medical record system. Patient characteristics including age, race or ethnicity, initial biopsy result, cancer stage, BMI, and known comorbidities will be collected.

Patient data for analysis will be captured using REDCap (Vanderbilt University). Paper forms including the SkinDex16 questionnaires will be kept in a locked cabinet in the Radiation Oncology offices and input into REDCap. Photos of patients' skin reaction will also be kept on this limited-access network drive. Patient information will be deidentified for final statistical analysis by removal of patient names and medical record numbers. Each patient will be assigned a study code at time of study registration.

Information gathered from the treatment planning system will include the V20 to V70 in 5 Gy increments reaching skin shell contours of "skin minus 3 millimeters" and "skin minus 5 millimeters" as well as the total dose. This will be collected for both simulation scans.

Statistical Methods

All analyses outside of the primary end point will be considered exploratory in nature. Chi square and *t* test will be used to evaluate differences in categorical and numerical values between arms. Subgroup analyses for BMI, total dose, and comorbidity will be conducted. We will also evaluate the incidence of RD for specific radiation skin dose stratification by reviewing the V20 to V70 in 5 Gy increments reaching a skin shell representing the thickness between the skin and the "skin minus 3 millimeters." This will be done on both the original dosimetry as well as a recalculated plan from the resimulation scan.

We will also evaluate any statistically significant differences in both the absolute numbers and relative changes of the laboratory values (CRP, TNF-α, IL-1β, and IL-6) at each of the

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3 time points in which they are drawn for each arm. All statistical tests will be 2-sided. We will report comparative data in good faith and emphasize that the primary intention of this study is to understand the safety and tolerability profile of Dermaprazole. All patients enrolled in this study who complete at least 60 Gy of radiation and follow up at 30 days post treatment will be included in the analysis. The principal investigator (PI; SD) will hold the full protocol, participant-level dataset, and statistical analysis code.

Exploratory subgroup analyses will examine treatment outcomes according to BMI, total radiation dose, and comorbidity status. Subgroup definitions and any covariate-adjusted models will be specified in the final statistical analysis plan before comparative outcome analyses are conducted. Given the limited sample size, subgroup analyses will be interpreted cautiously and may be restricted to descriptive summaries if participant numbers are insufficient for meaningful comparisons.

The extent and reasons for missing data will be summarized by treatment arm, and the number of evaluable participants will be reported for each analysis. Available observations will be used for exploratory analyses without imputation. Missing outcome assessments will not be interpreted as the absence of RD. Treatment discontinuation and loss to follow-up will be reported separately. Safety analyses will include all participants who received at least 1 application of their assigned topical treatment, including those who discontinued treatment early. The efficacy analysis described above will include participants who completed at least 60 Gy of radiation and the 30-day posttreatment follow-up assessment. Reasons for exclusion from this efficacy analysis will be reported by treatment arm.

Data Safety, Monitoring, and Audit

A data and safety monitoring plan (DSMP) is required for all protocols conducted at Mays Cancer Center. All protocols conducted at Mays Cancer Center are covered under the auspices of the Mays Cancer Center Institutional Data Safety Monitoring Plan. The Mays Cancer Center Institutional DSMP global policies provide individual trials with institutional policies and procedures for institutional data safety and monitoring, an institutional guide to follow, monitoring of protocol accrual by the Mays Cancer Center Protocol Review Committee, review of study forms, and orders by the Forms Committee, tools for monitoring safety events, oversight by the Data Safety Monitoring Committee (DSMC), and monitoring of unanticipated problem involving risks to participants or others by the Director of Quality Assurance (DQA) and DSMC, determining level of risk (priority of audit level score), and verification of protocol adherence via annual audit for all investigator initiated studies by the Mays Cancer Center Quality Assurance Division.

Safety and AE Outcomes

The PI will perform primary assessment of AEs, AE trends, and treatment effects on this study. The PI will conduct independent quarterly reviews and report findings to the Mays Cancer Center Data Safety Monitoring Board (DSMB) and the UT Health IRB. Baseline events and AEs will be captured using the Mays Cancer Center Master Adverse Events Document for each patient using CTCAE v5.0 for the grading and attribution of AEs. Usage of the Mays Cancer Center Master Adverse Events Document centrally documents the event and grades the seriousness of it, if the event was a change from baseline, determines the relationship between the event and study intervention, if the event was part of the normal disease process, and what actions were taken as a result of the event.

Expected AEs are those that have been previously identified as resulting from administration of topical or radiation therapy. For the purposes of this study, an AE is considered expected when the events are those related to systems within the radiation treatment field and include infection, allergy, or short- and long-term (greater than 6 months) skin changes. The common side effects of radiation to the head and neck most commonly includes RD (ie, erythema, blistering, and pigmentation changes) and fibrosis or firmness of the area in the long-term [25]. Commonly patients develop dry mouth, changes in taste, pain when swallowing, and weight loss [25,26]. Long-term, some patients can continue to have changes in taste and lymphedema [25-27].

The interventional cream is not yet tested in humans and reactions in vivo, especially in patients experiencing RD, are not yet known. Possible side effects include allergy to the topical or infection. Given the success in preclinical studies, it is unlikely that the interventional cream would lead to worsened rates of RD and skin integrity [21], although this is a possibility.

An attribution scale which will be used to attribute relatedness of the AE to the additional field, as determined by the treating investigator. Assignment of attribution is the responsibility of the treating investigator. Definite is when the AE is clearly related to the study treatment, probable is when the AE is likely related to the study treatment, possible is when the AE may be related to the study treatment, unlikely is when the AE is doubtfully related to the study treatment, and unrelated is when the AE is clearly not related to the study treatment.

All AEs will be recorded and reviewed by the study physician. Expected mild to moderate toxicity (grade 1-2) will be managed conservatively by the treating physician. Unexpected or severe AEs will be managed on a case-by-case basis at the discretion of the treating physician in coordination with the study team. Emergent dermatology consult and face-to-face evaluation within 48 hours will be sought for each suspected intervention-related AEs. Every effort will be made to continue radiation treatments for the prescribed duration, as would be the standard of care [28]. If the risks of continuation of any portion of the patients' treatment is felt to immediately outweigh the benefits or be detrimental to the patient, it may be temporarily withheld at the discretion of the treatment team. AEs directly related to Dermaprazole may prompt withdrawal from the study. Radiation will continue as scheduled unless grade 4 toxicity occurs, in which case delay to allow for healing is permitted.

Reporting Requirements

The AE collection or reporting period will begin with the first day of treatment with radiation or chemotherapy. AEs after study registration but prior to the first day of study treatment

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will be captured as ongoing concurrent secondary diagnoses and baseline symptoms present at the start of study. For this study, all master AE documents collected on patients for this protocol will be reviewed by the PI on a quarterly basis to determine if a serious safety problem has emerged that results in a change or early termination of a protocol, such as suspending enrollment due to safety or efficacy, or termination of the study due to a significant change in risks or benefits.

As per the Mays Cancer Center DSMP, any protocol modifications, problematic safety reports, unanticipated problems, and suspension or early termination of a trial must be reported to all members of the research team. Suspension and early termination of a trial must also be reported immediately to the DQA, who will promptly notify the sponsor and the UT Health IRB. The PI will review the Master Adverse Events documents to determine the significance of the reported events and will file the Investigator Initiated Study Annual DSMB Report Form on an annual basis with the Mays Cancer Center DSMB. The Investigator Initiated Study Annual DSMB Report Form includes information on AEs, current dose levels, number of patients enrolled, significant toxicities per the protocol, patient status (morbidity and mortality), dose adjustments with observed response, and any interim findings. Any trend consisting of 3 or more of the same events will be reported to the Mays Cancer Center DSMP for independent review outside of the annual reporting cycle, which begins 3 months following protocol start-up. Conflict of interest is avoided by the independent review of the Mays Cancer Center DSMB and by ongoing independent review of AEs trends by the DQA. All SAEs and unanticipated problem involving risks to participants or others will be reported following Mays Cancer Center and UT Health institutional guidelines.

Ethical Considerations

We confirm that informed consent will be obtained from all study participants according to the regulations outlined by the UT Health at San Antonio and the Mays Cancer Center Research Ethics Board and IRBs. The protocol, site-specific informed consent forms, and participant educational materials will also be reviewed and approved by the ethical review bodies. This study was approved by the UT Health Science Center at San Antonio IRB (IRB protocol 20210301HU). Written informed consent was obtained from all participants before study enrollment. Participant information is stored in secure institutional systems, including REDCap and limited-access network drives, and data used for analysis are deidentified through removal of direct identifiers and assignment of a study-specific code. Participants received no compensation for study participation.

Modification of the Protocol

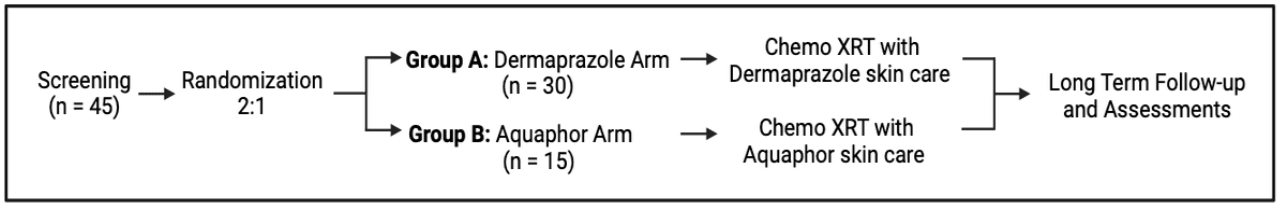
Any modifications to the protocol which may impact the study, potential benefit of the patient, or may affect patient safety will require a formal amendment to the protocol subject to approval by the ethics committee and IRB prior to implementation. All amendments will be agreed upon and approved prior to implementation.

Results

The study was registered on ClinicalTrials.gov (NCT04865731) and began participant recruitment in June 2022. The current protocol is version 12.0. A total of 4 participants received Dermaprazole at our center, with treatment initiated between July 2022 and February 2023. Their median age was 59 (range 52-74) years, with 2 male and 2 female participants. All 4 had squamous cell carcinoma of the tongue or base of tongue. Enrollment and study intervention have stopped at our center due to protocol-defined stopping criteria. Data collection is expected to be completed by 2027, followed by final data analysis and publication of the study results.

The study flow diagram is presented in Figure 1.

Figure 1. Study flow chart. XRT: Radiotherapy.



Discussion

This study will evaluate whether prophylactic topically reformulated esomeprazole, or Dermaprazole, reduces clinically significant RD in patients undergoing definitive radiation therapy for head and neck malignancies. We hypothesize that Dermaprazole will decrease the incidence and severity of CTCAE grade 2 or higher RD compared with Aquaphor. If supported, these findings would provide clinical evidence for repurposing topical esomeprazole as an adjunctive strategy to mitigate radiation-induced cutaneous toxicity and its associated morbidity.

The biologic rationale for esomeprazole is supported by preclinical studies demonstrating that PPIs possess anti-inflammatory and antifibrotic properties shown in preclinical studies [20]. Esomeprazole has been shown to modulate inflammatory pathways involving iNOS and other related inflammatory mediators [20]. More specifically, a preclinical model of radiation-induced skin injury, topical esomeprazole significantly attenuated dermal inflammation and fibrosis and was associated with reduced ulceration and necrosis and improved wound healing [20]. These findings provide the mechanistic and translational basis for evaluating Dermaprazole in patients exposed to therapeutic radiation.

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This study extends this work through a randomized comparison with Aquaphor and incorporates complementary measures of radiation-induced skin injury. In addition to CTCAE grading by the treating radiation oncologist, standardized clinical photographs will undergo blinded dermatologic assessment. Radiation dose-volume parameters within predefined skin contours will be evaluated to characterize associations between cutaneous radiation exposure and toxicity, while CRP, TNF-α, IL-1β, and IL-6 will be explored as potential inflammatory correlates. Patient-reported quality of life will provide an additional measure of the clinical burden of RD.

The focus on patients with head and neck malignancies was selected because this population is particularly susceptible to clinically significant RD due to the high cumulative radiation doses delivered to superficial tissues within the treatment field [29]. The study population was further restricted to patients receiving concurrent chemotherapy to reduce treatment heterogeneity and to evaluate Dermaprazole in a clinically relevant population undergoing definitive chemoradiation. Although these eligibility criteria improve internal consistency, they may limit generalizability to patients receiving radiation alone, altered radiation regimens, or other systemic therapies. If Dermaprazole demonstrates benefit in this setting, subsequent studies should evaluate its efficacy across broader populations with HNC and radiation treatment paradigms.

Several limitations should be considered. The single-center design and relatively small sample size may limit generalizability and the ability to detect uncommon toxicities or differences in delayed cutaneous outcomes. The 2:1 allocation produces a smaller control group than equal randomization, and variability in topical treatment adherence and individual radiation dose distributions may influence observed outcomes. Nevertheless, standardized treatment assessments, blinded dermatologic review, longitudinal follow-up, and incorporation of dosimetric and biomarker data strengthen the ability to characterize both the clinical and biological effects of the intervention.

If Dermaprazole demonstrates an acceptable safety profile and reduces clinically significant RD, larger multicenter studies will be warranted to confirm efficacy across broader radiation treatment settings and patient populations. Further investigation may also determine whether its anti-inflammatory and antifibrotic effects translate into reductions in chronic radiation-associated cutaneous changes. Study findings will be disseminated through peer-reviewed publication and presentation at scientific meetings following completion of data collection and analysis.

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Data Availability

The principal investigator and the research team will have access to the trial dataset. The raw data and materials from this study will not be publicly shared during this clinical trial. There are plans to use this study design and results for presentations at conferences and publication in pertinent journals.

Generative AI Use

The authors used ChatGPT (OpenAI; GPT-5.6 Sol) during manuscript revision to assist with language editing, clarity, organization, and formatting where appropriate. All AI-assisted content was reviewed, revised, and verified by the authors, who take full responsibility for the final manuscript.

Authors' Contributions

Conceptualization: YTG, MDB, TW, SD
Investigation: CJ, PR
Methodology: PB, YTG, MDB, TW, SO, SD
Project administration: CJ, PR, SD
Supervision: SD
Writing – original draft: AC
Writing – review and editing: AC, PB, YTG, MDB, TW, SO, SD
All authors reviewed and approved the final manuscript

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Conflicts of Interest

YTG is an inventor on patents, owned by Stanford University and Baylor College of Medicine, that protect the use of proton pump inhibitors (PPIs) for therapeutic use of new indications. The other authors have no conflicts of interest to declare.

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Abbreviations

ADL: activities of daily living
ADMA: asymmetric dimethylarginine
AE: adverse event
CITI: Collaborative Institutional Training Initiative
CRP: C-reactive protein
CT: computed tomography
CTCAE: Common Terminology Criteria for Adverse Events
DDAH: dimethylarginine dimethylaminohydrolase
DQA: Director of Quality Assurance
DSMB: Data and Safety Monitoring Board
DSMC: Data Safety Monitoring Committee
DSMP: data and safety monitoring plan
ECOG: Eastern Cooperative Oncology Group
GCP: Good Clinical Practice
HNC: head and neck cancer
ICAM-1: intercellular adhesion molecule 1
IL: interleukin
iNOS: inducible nitric oxide synthase
IRB: Institutional Review Board
NCI: National Cancer Institute
NF-κB: nuclear factor kappa B
NO: nitric oxide
NOS: nitric oxide synthase
PI: principal investigator
PPI: proton pump inhibitor
RD: radiation dermatitis
RTOG: Radiation Therapy Oncology Group
SAE: serious adverse event
TNF: tumor necrosis factor
UT: University of Texas
VCAM-1: vascular cell adhesion molecule 1

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