

RADIATION THERAPY ONCOLOGY GROUP

RTOG 97-13

**PHASE III RANDOMIZED STUDY COMPARING BEST SUPPORTIVE CARE TO BIAFINE®
AS A PROPHYLACTIC AGENT FOR RADIATION-INDUCED SKIN TOXICITY FOR
WOMEN UNDERGOING BREAST IRRADIATION**

Study Chairs

Oncology Nurse

Jackie Fisher, R.N., B.S.N.
Wayne State University
Radiation Oncology Center
Oakwood Hospital
18101 Oakwood Boulevard
Dearborn, MI 48123
(313) 593-7335
FAX # (313) 593-8844

Radiation Oncology

Randy Stevens, M.D.
(212) 263-5055
FAX# (212) 263-6274

Quality of Life

Charles Scott, Ph.D.
(215) 574-3208
FAX# (215) 928-0153

Activation Date:

February 1, 1998

Current Edition:

**April 17, 1998
Includes Revision 1**

This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.

INDEX

Schema

Eligibility Check

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Patient Selection
- 4.0 Pretreatment Evaluation
- 5.0 Registration
- 6.0 Protocol Treatment
- 7.0 Drug Therapy
- 8.0 Surgery
- 9.0 Other Therapy
- 10.0 Pathology
- 11.0 Patient Assessment
- 12.0 Data Collection
- 13.0 Statistical Considerations

References

- Appendix I - Sample Consent
- Appendix II - Karnofsky Performance Status
- Appendix III - RTOG and ONS Skin Toxicity Criteria
- Appendix IV - Patient Instructions for Biafine Application
- Appendix V - Patient Instructions for Institutional Preference
- Appendix VI - Product Log
- Appendix VII - Study Product Shipping Form

**RADIATION THERAPY ONCOLOGY GROUP
RTOG 97-13**

**PHASE III RANDOMIZED STUDY COMPARING BEST SUPPORTIVE CARE TO BIAFINE AS A
PROPHYLACTIC AGENT FOR RADIATION-INDUCED SKIN TOXICITY FOR WOMEN
UNDERGOING BREAST IRRADIATION.**

SCHEMA

S	<u>Total Dose</u>	R	<u>Arm1</u>	Best Supportive Care
	1. ≥ 50.0 to < 59.0 Gy			<i>(Institution Preference other than</i>
R	2. ≥ 59.0 to 64.0 Gy	A		<i>Biafine)</i>
T		N	<u>Arm 2</u>	Biafine
	<u>Bra Size</u>	D		
R	1. 32A,B; 34A,B; 36A	O		
	2. 32C; 34C; 36B,C; 38A,B,C	M		
A	3. Larger	I		
T		I		
I		Z		
F		E		
Y				

Treatment: Patients will apply assigned product following their first radiation treatment and will continue for 2 weeks post RT. Agent will be applied three times a day but not less than 4 hours before the daily radiation session. Agent will be applied seven days a week. Institutional preference (*Arm 1*) may include no treatment, but may not include Biafine.

Eligibility (See Section 3.0 for details)

- Histologically confirmed diagnosis of breast carcinoma
- No rash, ulceration, bleeding, or unhealed scar in treatment area
- Minimal dose - 50.0 Gy including boost
- KPS ≥ 70
- No medical contraindication (*allergy or sensitivity*) to Biafine or to the planned supportive care.
- No prior RT, chemotherapy, or mastectomy
- No concurrent chemotherapy (*hormones allowed*).
- Ability to follow and comply with treatment regime.
- No skin involvement by tumor
- Use of bolus is prohibited
- No history of, or current, connective tissue disorders.
- Study-specific consent form

Institution # _____

RTOG 97-13

ELIGIBILITY CHECK (2/1/98)

Case # _____

- _____(Y) 1. Does the patient have a histologically confirmed carcinoma of the breast?
- _____(N) 2. Has the patient had a prior mastectomy, chemotherapy, or radiation to treatment area?
- _____(N) 3. Does the patient have a history of, or current, connective tissue disease?
- _____(N) 4. Does the treatment area have any skin problems as specified in Section 3.2.1 and 3.2.3?
- _____(N) 5. Is there any skin involvement by tumor?
- _____(≥ 18) 6. What is the patient's age?
- _____(≥ 70) 7. What is the Karnofsky status?
- _____(N) 8. Is concurrent chemotherapy planned?
- _____(N/NA) 9. Is there a known allergy to Biafine or to the product favored by institution (*code NA if institution preference is no treatment*)?

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*)
 _____ Total Dose (*³50.0 Gy to < 59.0 Gy vs. ³59.0 Gy to 64.0 Gy*)
 _____ Bra Size (*32A,B; 34 A,B; 36A vs. 32C; 34C; 36B,C; 38A,B,C vs. Larger*)
 _____ Birthdate
 _____ 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

According to the American Cancer Society there will be an estimated 180,200 new cases of invasive breast cancer in 1997. Radiation therapy to the breast is employed following breast conserving surgery for early stage cancers as well as selected ductal carcinomas in-situ. It is also used as pre-operative treatment for patients with unresectable locally advanced disease, and recurrent breast cancer.¹ During a course of radiation temporary skin reactions are common and vary from mild erythema to brisk, moist desquamation. The severity of skin toxicity is dependent on volume of tissue treated, total daily dose, fractionation, dose distribution, and certain individual factors.² These reactions are commonly treated with local measures (*i.e. creams, gels etc.*) and occasionally may require a treatment break. Skin reactions associated with radiation therapy may impose significant discomfort and may interfere with the patient's daily living activities.

A recent review of the literature for radiation induced skin toxicity clearly demonstrated that no standard of care for the prevention or intervention of radiation-induced skin toxicity exists, and that intervention is primarily based on the clinician clinical experience. A random survey of RTOG institutions revealed that 50% of the RTOG institutions surveyed utilize Aloe Vera Gel as the treatment of choice for mild to moderate radiation induced dermatitis, while the remainder of institutions utilized Aquaphor, or other products such as Carasyn gel, Lanolin etc. Although much attention has been given to how radiation therapy affects the skin, until recently little research has been performed in identifying and standardizing clinical intervention. Clinically, the emphasis has been on teaching self care to minimize skin trauma, irritation, and/or infection.

A study in press by the North Central Cancer Treatment Group reported that Aloe Vera Gel did not protect against radiation-induced dermatitis when used prophylactically in women undergoing breast irradiation.³ Another study performed in 1990 at Rush-Presbyterian-St. Luke's Medical Center, utilizing the product "Natural Care Gel," with major ingredients Aloe Vera, and D-panthenol, for women undergoing breast irradiation, demonstrated little change in erythema or desquamation but did provide relief from burning and itching.⁴

Biafine, a wound healing product from France, was approved in 1995 by the FDA for use in the U.S. It has reportedly been the product of choice in France for radiation induced dermatitis for two decades. A comparative study of Biafine performed in 1973, at the Regional Centre for Combating Cancer, at Marseille Hospital, France, concluded that Biafine was twice as effective as the best alternative treatment for preventing and treating radiation skin reactions.⁵ Another study concluded that Biafine enhances the first stage of the healing process by recruiting macrophages and acts on the production of granulation tissue.⁶

Earlier trials testing such agents as topical vitamin C and topical cortisone cream have demonstrated no discernible benefit in preventing radiation induced dermatitis.^{7,8}

There are many factors that influence the effects of radiation: site, time-dose volume relationships, radiation type and energy, nutritional status and individual patient factors (*i.e. complexion.*) Thus, it will be important to control for these factors.

In today's health care setting, the importance and consideration of cost containment cannot be discounted. Thus, it is important to monitor cost/benefit ratios due to the variance among product costs.

At the present time, there is no standard of care for decreasing or preventing radiation-induced dermatitis. Presently, there are numerous products being used by radiation oncology departments in the U.S. Based on the results of the NCCTG and Rush-Presbyterian studies and the introduction of a new skin care product (*claiming*) efficiency in preventing radiation-induced dermatitis, this study is designed to compare other products with Biafine in preventing radiation-induced dermatitis. It is hypothesized that Biafine will be a prophylactic agent for radiation dermatitis in women undergoing breast irradiation.

Assessment of skin reactions are essential to this study. There is evidence that patients and clinicians differ in their assessment of the severity of toxicities.⁹ In order to assess the effectiveness between Biafine and other supportive care, this trial will utilize clinician assessments and patient self-assessments using the Spitzer Quality of Life skin questionnaire.

Alleviation of symptoms and/or toxicities has, at times, been considered a surrogate for improved quality of life. In order to compare the effect upon quality of life between best supportive care and Biafine, this trial will utilize the Spitzer Quality of Life Index (*SQLI*). The *SQLI* is a five item categorical questionnaire summed in a Likert format with total scores ranging from 0-10. There are no subscale scores for the *SQLI*. The reliability and validity have been established.¹⁰ The *SQLI* has been criticized because it does not assess symptoms which is the reason for pairing it with the patient self-assessment of skin reactions. The *SQLI* has been used in testicular patients,¹¹ gastric patients,¹² terminal patients,¹³ glioma patients,¹⁴⁻¹⁵ lung, ovary and breast cancer patients.¹⁶ The *SQLI* has been applied as both a rater-assessed form and a patient self-assessment form. We will be using the *SQLI* as a patient self-assessment form. This trial will examine the following quality of life hypothesis: does a clinically meaningful reduction in skin toxicities correlate with improved quality of life.

2.0 OBJECTIVES

- 2.1 To determine whether Biafine is most effective in preventing and reducing radiation-induced dermatitis in selected women undergoing breast irradiation.
- 2.2 To determine maximum reported severity, time to occurrence, and duration of dermatitis.
- 2.3 To compare patients' quality of life between interventions.
- 2.4 To assess product toxicities.

3.0 PATIENT SELECTION

3.1 Patient Eligibility

- 3.1.1 Histologically-confirmed diagnosis of breast cancer.
- 3.1.2 Patients will receive at least 50 Gy total dose to primary site.
- 3.1.3 Treatment plan cannot include concurrent chemotherapy; hormones are allowed.
- 3.1.4 Age \geq 18.
- 3.1.5 Karnofsky performance status \geq 70.
- 3.1.6 Patient must be able to comply with treatment schedule.
- 3.1.7 Patient must sign a study-specific informed consent form.

3.2 Patient Ineligibility

- 3.2.1 Unhealed, bleeding or ulcerating wound in treatment area.
- 3.2.2 Known allergy to Biafine or to other products preferred by institution.
- 3.2.3 Rash, ulcerations or poorly healed scars in treatment area.
- 3.2.4 Involvement of skin by tumor.
- 3.2.5 Use of bolus.
- 3.2.6 History of, or current, connective tissue disease.
- 3.2.7 Prior radiation to treatment area, mastectomy, or chemotherapy.

4.0 PRETREATMENT EVALUATION (4/17/98)

- 4.1 Baseline color photo of treatment site (*polaroid or 35 mm[3x5 or 4x6]*).
- 4.1.1 Distance: 30 inches (*2.5 feet*).
- 4.1.2 Angle: Standing directly in front of patient, from below up to fold.
- 4.1.3 Lighting: Use flash on camera (*same lighting for all patients*).
- 4.1.4 Patient should be lying flat with arm of affected side extended over her head to reveal axilla.
- 4.1.5 Photo is not to include the patient's face.
- 4.1.6 All photos must be dated and identified by study and case numbers using the B1 Form.
- 4.1.7 Photos are sent to the study chair, J. Fisher, and not to RTOG Headquarters.
- 4.2 Documentation of bra size prior to randomization.
- 4.3 Documentation of planned total radiation dose prior to randomization.
- 4.4 Completion of pretreatment patient questionnaires.

5.0 REGISTRATION PROCEDURES

- 5.1 Each institution must submit a Study Product Shipment Form (*Appendix X*) to RTOG Headquarters prior to the randomization of its first case. Allow adequate processing time (*7-10 days*) before calling to register your first case.
- 5.2 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
- Treatment Start Date

6.0 RADIATION THERAPY

6.1 Physical Factors

- 6.1.1** *Equipment:* Linear accelerator with 4-6 MV photon therapy. Electron beam therapy shall be used for the boost to the primary tumor bed. A brachytherapy boost is not permitted in this study.
- 6.1.2** Selection of the appropriate electron energy for the boost portal should be based on the depth of the primary lesion.
- 6.1.3** Treatment distance should be 100 SAD (*preferable*) or ≥ 80 SSD.
- 6.1.4** Bolus will not be used.

6.2 Localization Requirements

- 6.2.1** *Simulation:* Simulation of the tangential breast portals is highly recommended. Use of a breast bridge or other planning device is less preferable. Simulation of the boost portal (*with a solder wire delineating the field*) is preferred. If the field is planned without a simulator, a polaroid with the boost field clearly delineated on the patient's skin is required. **Copies of simulation films of each field and initial port films will be sent to RTOG Headquarters ONLY if requested.** The calculation form, isodose distribution, and treatment prescription will be sent to RTOG Headquarters at the end of treatment for quality assurance review. The calculation form for the electron boost portion of treatment will also be sent to RTOG Headquarters at the end of treatment.
- 6.2.2** *Verification:* Beam verification (*port*) films must be obtained for each field at least every 2 weeks during treatment and when any adjustments are made. Port films of each field will be submitted to the RTOG Headquarters only if specifically requested.

6.3 Dose Fractionation

- 6.3.1** *Tangential Breast Portals:* The dose to the prescription point will be 46.0 Gy at 2.0 Gy/day, five days per week. If the homogeneity is $> 10\%$, it is permissible to deliver 50.4 Gy at 1.8 Gy/day. The radiation therapy study chair shall be contacted before treatment commences.
- 6.3.2** *Electron Boost Portal:* The electron boost will be delivered at 2.0 Gy/day. The total dose to the tumor bed (*including the photon and electron treatment portals*) shall be ≥ 60.0 Gy (*i.e. 46.0 Gy to the tangential breast portals and 14.0 Gy to the electron boost portal*). The recommended total dose to the tumor bed is 60.0 Gy. The maximum permissible dose to the tumor bed is 64.0 Gy.

6.4 Target Volume Irradiation Portals

- 6.4.1** *Tangential Breast Portals:* A minimum of 1 cm margin should be placed around the ipsilateral breast. The treatment portal should include the ipsilateral breast and margin and encompass the chest wall on the simulation field. Use of a breast (*slant*) board or similar treatment device is encouraged to reduce the curvature of the chest wall and keep the widest portion of lung, as visualized on the simulation films, to ≤ 3 cm.
- 6.4.2** *Breast Boost Portal:* If surgical clips have been placed in the tumor bed, the boost portal should encompass the clips and the incision with a minimum 1 cm margin. If surgical clips have not been placed, the target volume should encompass the incision and a 3 cm margin.

6.5 Dose Calculation

- 6.5.1** For the tangential portals, dose shall be prescribed to the minimum isodose line encompassing the chest wall and breast at the level of the central axis. Wedges should be used to minimize inhomogeneity. The maximum permissible inhomogeneity is $+10\%$ (*negative values are not allowed*). Notify the radiation therapy study chair if larger dose heterogeneity is expected. The dose at 2 mm depth (*below skin surface*) should be $\geq 95\%$ of the prescription point. The use of bolus material is not allowed.
- 6.5.2** For the boost portal, an appropriate electron energy should be chosen to encompass the target volume within the $\geq 90\%$ isodose line.

7.0 PROTOCOL TREATMENT

7.1 Product Information: Biafine

7.1.1 Biafine has been used in France for over 20 years. Its indication for use has been to treat all types of wounds, from minor abrasions and sunburns to major thermal wounds, radiation dermatitis, pressure ulcers and diabetic leg ulcers. Biafine is a pleasant fragrant non-toxic cream, It is a non-prescription product.

7.1.2 Pharmakinetics

Biafine enhances the first stage of the healing process by recruiting a significant number of macrophages, acts on the production of granulation tissue, and has an indirect action on epithelialization.

7.1.3 Supply

Supplied by Médix Pharmaceuticals Americas; available in 1.5 oz (42.0g) and 0.66 oz (18.6g) lined tubes, 12 and 24 tube cases.

7.1.4 Ingredients

Biafine consists of purified water, liquid paraffin, glycol monostearate, stearic acid, propylene glycol, paraffin wax, squalene, avocado oil, trolamine sodium alginate, cetyl palmitate, methylparaben, sorbic acid, propyl paraben, and fragrance.

7.2 Application (4/17/98)

Arm 1: Institutions will record their product preference (*other than Biafine*) on the onstudy form (I1). Preference may include no treatment. Patients will begin applying the product of choice immediately after their first RT treatment. The product must be applied three times a day seven days a week and will be continued for two weeks after completion of RT. The patient will be instructed not to apply the product less than four hours prior to the daily treatment. One of the three daily applications should be done immediately following the daily radiation treatment and one can be done at bedtime. The treatment area should be gently cleansed prior to each application to prevent product build up.

Arm 2: Apply as above, utilizing Biafine.

7.3 Treatment Modification.

7.3.1 If necessary, other treatments (*i.e. addition of hydrocortisone cream*) may be added. Documentation of treatment prescribed and delivered is required.

Protocol treatment is to be discontinued **immediately** if an allergic response, moist desquamation or bleeding occurs.

7.3.2 Grade 3 and 4 skin toxicities (*Appendix III*) will be reported immediately to HQ and the study chair. The protocol agent will be discontinued. Further treatment will be at the physicians's discretion.

7.4 Distribution (4/17/98)

7.4.1 The Study Product Shipping Form (*Appendix VII*) must be completed and returned to RTOG Headquarters prior to randomizing any patient on study. Allow adequate processing time (*7-10 days*) before calling to randomize your first patient.

7.4.2 Medix Pharmaceuticals will supply both Biafine and aloe vera gel (*CVS[®] and Fruit of the Earth[®]*) to the person designated on the Study Product Shipping Form. Other products may be used for Arm 1 but their cost will be responsibility of the individual institution or patient. Products are to be distributed only to patients randomized to this study. The product log in Appendix VI will be used to record both the receipt of any product shipments from Medix Pharmaceuticals and the dispensing of product to the patient.

7.4.3 Additional product during the accrual phase of this study may be ordered directly from Medix Pharmaceuticals. See Section 7.4.4.

7.4.4 At the completion of this study all unused products will be returned to:

**Médix Pharmaceuticals, Americas, Inc.
6301 Ivy Lane**

Suite 5100
Green Belt, MD 20770
(800) 672-7811 ext. 10
FAX (301) 479-1725

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Not applicable to this study.

10.0 PATHOLOGY

Not applicable in this study.

11.0 PATIENT ASSESSMENT

11.1 Study Parameters

Study	Pre Entry	Weekly	Post Treatment
Skin Assessment, KPS, Wt.	X	X	X
Spitzer QLI	X	X	X ^b
Patient Self Questionnaire	X	X	X ^b
Color Photo	X	X ^a	X ^b

- a. Upon appearance of skin toxicity \geq grade 2 and weekly until reaction subsides.
- b. At end of RT and at 2 and 6 weeks after RT completion. See Sections 12.2-3 for submission schedule.

11.2 Criteria for Discontinuing Therapy

- 11.2.1 The development of allergic response to protocol agent.
- 11.2.2 The development of bleeding or moist desquamation at treatment site.
- 11.2.3 Developing a grade 3-4 skin toxicity.

11.3 Patient Assessments (4/17/98)

- 11.3.1 Skin assessments will be done prior to treatment, weekly during radiation therapy and at two and six weeks post RT by the physician or their designate utilizing the RTOG Acute Radiation Morbidity Scoring Criteria for skin and the ONS Breast Scoring Toxicity.
- 11.3.2 A color photo is required pre-treatment, at the time of grade \geq 2 reaction, at the end of treatment, and at the two and six week follow-up. Indicate on the B1 Form whether the photo was taken for toxicity. Remember to record the date of the photograph on the B1 Form.
- 11.3.3 Patients will complete a self assessed skin questionnaire and the Spitzer Quality of Life Questionnaire pre-treatment and weekly during RT, at end of RT, and at weeks 8 and 12 from start of treatment.
 - 11.3.3.1 The SQLI and self-assessment skin toxicity forms are completed pretreatment, weekly during radiation therapy, and at 2 and 6 weeks post radiation therapy.
 - 11.3.3.2 The forms should be completed every Friday during treatment but on no specific day at weeks 2 and 6 post treatment.
 - 11.3.3.3 Review the questionnaires and instructions with the patient and significant other or family.
 - 11.3.3.4 Review the scheduled intervals at which the questionnaires are required.

12.0 DATA COLLECTION (4/17/98)

12.1 Summary of Data Submission

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

Item

- Demographic Form (A5)
- Initial Evaluation Form (I1)
- Pre-treatment Physician Skin Assessment (F2)
- Pre-treatment Quality of Life (PQ)

Due

Within 2 weeks of study entry

Cosmesis Photo (B1)

Radiotherapy Form (T1)
Treatment Prescription (T2)
Isodose Distribution (T6)
Calculation Form (TL)
Cosmesis Photo (B1)

End of RT

Cosmesis Photo (B1)
Follow-up Form (F1)

At 2 and 6 weeks post RT

Treatment Quality of Life Forms (PF)
Physician Skin Assessment (F2)

At 6 weeks post RT

12.2 Submission of Photographs

Cosmesis photos (B1) will not be collected at RTOG. Send directly to Jackie Fisher RN, Wayne State University, Radiation Oncology Center, Oakwood Hospital, 18101 Oakwood Blvd., Dearborn, MI 48123. All photos must be attached to a completed B1 form. Use tape; do not staple.

12.3 Form Completion

12.3.1 The PQ is the pre-treatment set of quality of life forms, containing a Spitzer quality of life form and a patient skin self assessment form. The PQ is submitted within 2 weeks of study entry.

12.3.2 The PF is the treatment and follow up set of quality of life forms. Each week during treatment, and at 2 and 6 weeks post RT, the patient will complete the two forms preferably at the same time. After the 6 week post treatment assessment submit all forms together to HQ with one PF cover sheet. Please make certain that the date and week is on each assessment form. If a week was missed, note this with a reason on the cover sheet. Since this is the endpoint of the study, patients must complete these forms regularly.

12.3.3 The F2 is the physician pre-RT skin assessment form and is in flowsheet format. The pre-treatment skin assessment must be recorded PRIOR to ANY RT, and is submitted to HQ within 2 weeks. The date of the pretreatment assessment is required on the form. The weekly treatment assessments are completed on a separate F2. The physician will complete a column each week during treatment and at 2 and 6 weeks post RT. Submit to HQ following the 6 week post treatment assessment.

12.4 Institutional Charts

Working flowsheets for institutional charts can be obtained by calling Jackie Fisher. Please note drug distribution column for weekly monitoring of distribution to patient.

12.5 Product Log (Appendix VI)

A copy of the product log will be sent to Jackie Fisher at the completion of the study.

13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 The primary endpoint is the reduction and prevention of skin acute toxicities.

13.1.2 Quality of life will be assessed using the SQLI.

13.2 Sample Size

13.2.1 *Skin Toxicity Endpoint*

The primary endpoint of this trial is the reduction or prevention of skin toxicities. This endpoint will primarily be assessed by medical professionals using the RTOG acute skin radiation toxicity scale. Additionally, a patient self-assessment of skin reaction will be completed. Skin assessments will be performed weekly and the worst toxicity reported will be used to compare treatments for the primary endpoint.

Radiation therapy alone is assumed to cause the following level of toxicity.

Grade of Skin Toxicity				
0	1	2	3	4

13%	52%	32%	2%	1%
-----	-----	-----	----	----

Toxicity data is ordered categorically, and Whitehead’s sample size formula for this type of data was employed.¹⁷ Assuming that the application of Biafine during radiotherapy reduces the incidence of grade 2-4 skin toxicity by 57%, we can estimate all probabilities as follows:

Estimated Incidence on the Biafine Arm Grade of Skin Toxicity				
0	1	2	3	4
31%	54%	14%	1%	0%

Setting the significance level at 95% (*two-sided*) and statistical power at 90% the estimated sample size is 62 patients per arm. In order to ensure that the required sample size is analyzable an additional 10% will be required to adjust for ineligible and unanalyzable (*patients with no data submitted*) cases. Therefore, 68 cases per arm will be required or a **total of 136 randomized patients**. This sample size will ensure a 90% ($\alpha=0.10$, *type II error*) probability of detecting a relative 57% decrease in acute skin toxicity while rejecting the null hypothesis at the 95% level ($\alpha=0.05$, *two-sided type I error*).

13.3 Patient Accrual

The following table displays the length of time necessary to accrue 136 patients given different average monthly accruals.

<u>Average Monthly Accrual</u>	<u>Time to Accrue 136 Patients</u>
12.0	1 year
10.0	1.2 years
8.0	1.5 years
4.0	2.9 years

The average monthly accrual is expected to be 8 patients per month. Thus it will take 1.5 years to complete the accrual phase of this study. However, if the monthly accrual is less than 4 patients per month, study feasibility will be re-evaluated.

13.4 Randomization Scheme

The treatment allocation will be done using a randomized permuted block within strata to balance patient factors other than institution. Patients will be stratified by total radiation dose and breast size. There will be a check on the balance of treatment assignments within each institution. Patients will be assigned with equal probability to each treatment by the RTOG.

13.5 Analysis Plans

13.5.1 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:

- i) the patient accrual rate with projected completion date for the accrual phase;
- ii) the distribution of patients with respect to pretreatment characteristics;
- iii) compliance rate of treatment delivery with respect to the protocol prescription;
- iv) the frequency and severity of the toxicities by treatment arm.
- v) compliance with the submission of the SQLI and the patient skin self-assessment form.

13.5.2 Interim Analyses of Study Endpoints

There will be two interim analyses of worst observed skin toxicities within 90 days from the start of treatment. At each interim analysis boundaries for rejecting the null hypothesis (H_0) of no difference and for rejecting the alternative (H_1) of a 57% decrease in acute grade 2 or worse skin toxicities are set. The log-likelihood statistic will be used. If the significance level exceeds (*smaller*) the H_0 boundary

then it will be rejected and the study will proceed to examining the tumor relapse endpoint. If the significance level exceeds (larger) the H1 boundary then it will be rejected and a recommendation of termination of accrual will be given to the RTOG Data Monitoring Committee (DMC). The interim analyses will proceed according to the table below.

Total Evaluable Followed for 3 months	H0 Boundary Significance Level	H1 Boundary Significance Level
68	0.0029	0.25
102	0.009	0.09
136	0.05	0.05

13.5.3 Analysis and Reporting of Initial Treatment Results

The major analysis will be undertaken when all patients have been potentially followed for a minimum of three months from date of entry. 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 of institutional accrual;
- c) distribution of the important prognostic factors by assigned treatment;
- d) observed results with respect to the study endpoints.
 - i. Maximum skin toxicity reported.
 - ii. Time to development of grade 2 or worse skin toxicities, evaluated by cumulative incidence.
 - iii. The SQLI, worst toxicity at a time point, and patient self-assessment of skin reactions will be compared at week 4 of RT, end of RT, and at 8 and 12 weeks from the start of RT to answer the quality of life hypothesis. This comparison will be performed both across and within (*if there is a significant difference in toxicity*) treatment arms. Patients with reduced skin toxicity (*grade 0-1*) versus higher skin toxicities will be correlated with improvement in SQLI (*also defined as a 1 point improvement*). Fisher’s test will be used.

13.6 Planned Gender and Minority Inclusion

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female			13	5	118		136
Male							
Unknown							
Total			13	5	118		136

REFERENCES

- 1, 2. Coia, Lawrence, MD and David Moylan, III, MD; Introduction to Clinical Radiation Oncology, Medical Physics Publishing, Madison, Wisconsin, 1991 pp. 162, 179.
3. Burk, M., RN. Et al. Phase III Evaluation of Aloe Vera Gel as a Prophylactic Agent for Radiation Induced Skin Toxicity. Abstract. Proceeding of 35th Annual ASTRO Meeting. 1126.
4. Witt, ME, McDonald-Lynch A., Lydon J. Enhancing Skin Comfort During Radiation Therapy. Oncology Nursing forum. Vol. 17, no. 2, p. 276, 1990.
5. Spitalier, JM., MD, and Robert Amalric, MD. "Value of Biafine in the Prevention and Treatment of Skin Reactions Following Radiotherapy." Centre regional DeLutte Centre LeCancer, Marsille, France. Unpublished manuscript. 1973
6. Dubertret, Prof. Healing: Clinical Pharmacological Study Summary. Unpublished manuscript. 1994.
7. Halperin EC, Gaspar, L., George, S., Dear, D., and Pinnel, S. Double Blind, Randomized Prospective Trial to Evaluate topical Vitamin C Solution for Prevention of Radiation Dermatitis. International Journal of Radiation Oncology, Biology Physics, 26: 413-416, 1993.
8. Potera, ME, Lookingbill DP, Stryker, JA Prophylaxis of radiation Dermatitis with Topical Cortisone Cream. Radiology 143: 775-777, 1982.
9. Watkins-Bruner D, Scott C, Lawton C, DelRowe J, Rotman M, Buswell L, Beard C and Cella D: RTOG's First Quality of Life Study - RTOG 90-20: A Phase II Trial of External Beam Radiation with Etanidazole for Locally Advanced Prostate Cancer. Int J Radiat Oncol Biol Phys 33:901-906, 1995.
10. Spitzer WO, Dobson AJ, Hall J, Chesterman E, Levi J, Shepherd R, Battista RN, Catchlove BR: Measuring the quality of life of cancer patients: a concise QL-index for use by physicians. J Chronic Dis 34(12):585-97, 1981.
11. Tamburini M, Filiberti A, Barbieri A, Zanoni F, Pizzocaro G, Barletta L, Ventafridda V: Psychological aspects of testis cancer therapy: a prospective study. J Urol Dec;142(6):1487-9, 1989.
12. Buhl K, P Schlag, C Herfarth: Quality of life and functional results following different types of resection for gastric carcinoma. Eur J Surg Oncol 16:404-409, 1990.
13. Addington-Hall JM, MacDonald LD, Anderson HR: Can the Spitzer Quality of Life Index help to reduce prognostic uncertainty in terminal care? Br J Cancer Oct;62(4):695-9, 1990.
14. Awwad S, Cull A, Gregor A: Long-term survival in adult hemispheric glioma: prognostic factors and quality of outcome. Clin Oncol (R Coll Radiol) Nov;2(6):343-6, 1990.
15. Bauman GS, Gaspar LE, Fisher BJ, Halperin EC, Macdonald DR, Cairncross JG: A prospective study of short-course radiotherapy in poor prognosis glioblastoma multiforme. Int J Radiat Oncol Biol Phys 29:835-839, 1994.
16. Ovesen L, Allingstrup L, Hannibal J, Mortensen EL, Hansen OP: Effect of dietary counseling on food intake, body weight, response rate, survival, and quality of life in cancer patients undergoing chemotherapy: a prospective, randomized study. Ovesen L et al. JCO 11:2043-2049, 1993.
17. Whitehead J: Sample size calculations for ordered categorical data. Stat Med 12:2257-2271, 1993.

APPENDIX I

RTOG 97-13

PHASE III RANDOMIZED STUDY COMPARING BEST SUPPORTIVE CARE TO BIAFINE® AS A PROPHYLACTIC AGENT FOR RADIATION-INDUCED SKIN TOXICITY FOR WOMEN UNDERGOING BREAST IRRADIATION

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 I have an opportunity to decide whether or not to undergo the procedure after knowing the risks, benefits, and alternatives involved. 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

The purpose of this research study is to determine if a skin care cream is effective in preventing the skin reaction caused by radiation therapy.

DESCRIPTION OF PROCEDURES (4/17/98)

This study involves at random (*by chance*) assignment to one of two skin care approaches. It is not clear at the present time which is better. For this reason, the choice will be based upon a the method of selection called randomization. Randomization means that my physician will call a statistical office which will assign me one of the products by computer. The chance of my receiving one of the two is approximately equal. I will be assigned to either Biafine or to another treatment selected by my physician. If I am not randomized to Biafine, my physician may opt to not use any cream at all until I have a skin reaction from the radiation.

I will gently massage cream into the radiation-treated area of my breast three times each day seven days a week. I will begin after my first radiation treatment and will continue for two weeks after treatment ends. I must not apply the skin care product less than four hours before my daily radiation treatment. One of the daily applications should be right after my daily radiation treatment, another at bedtime, and the third at my convenience as long as it's at least 4 hours daily before my radiation treatment.

Médix Pharmaceuticals Americas (*MPA*) will provide me with Biafine at no charge. They will also provide aloe vera gel unless my physician prefers that I use something else. Unless my physician provides me with the product of his or her choice, the cost of anything besides Biafine and aloe vera gel will be my responsibility.

My physician or his/her designates will evaluate my skin in the treatment area before treatment begins, weekly during radiation, then twice after radiation treatments end. I will be asked to fill out two patient questionnaires pre-radiation, weekly during radiation and at two follow-up visits after radiation. I will also have photos taken of my breast pre-radiation, at completion of treatment and then six weeks later. If I develop a moderate skin reaction from the radiation, I will need to have photos taken until the reaction goes away. My identity will not be revealed in these pictures or in statements describing the pictures. These photos will not include my face.

RISKS AND DISCOMFORTS

The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring. The treatments used in this study may cause some, all or none of the following side effects.

Reported side effects from Biafine are rare. They have mainly been allergic skin reactions, causing itching and/or rash which usually is resolved by stopping application. If Biafine is used incorrectly (*applied less than four hours before the daily radiation treatment*), it can cause or worsen a skin reaction.

My physician will check my condition closely as part of this treatment. I will permit my doctor or designated nurses to assess my treatment area frequently.

If I am using another product, the side effects include: (*must be added by treating institution*).

CONTACT PERSONS

In the event that injury occurs as a result of this research, treatment will be available. 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 addition, I may contact _____ at _____ for information regarding patients' rights in research studies.

BENEFITS

The purpose of this research study is to develop improved methods of lessening skin reactions to radiation treatment. At the present time, no definite statement can be made as to what extent my participation will be directly beneficial to me. I need not participate in this study to remain under my doctor's care.

ALTERNATIVES

The current alternative to this study treatment is a variety of other skin care products when skin reactions occur.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I am free to withdraw my consent to participate in this program at any time. 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, my participation has been voluntary.

CONFIDENTIALITY

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 applicable 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.

I have read all of the above, asked questions, received answers concerning areas I did not understand. I 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
RTOG ACUTE RADIATION MORBIDITY CRITERIA**

	[0]	[1]	[2]	[3]	[4]
SKIN	No change over baseline	Follicular, faint, or dull erythema/epilation/dry/desquamation/decreased sweating	Tender or bright erythema, patchy moist desquamation/moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis

ONS BREAST ASSESSMENT SCORING CRITERIA

COMFORT ALTERATION

Fatigue:

- 0 - None, able to carry on daily routine
- 1- Able to carry on daily routine with rest periods and earlier bedtime
- 2- Must curtail daily activities even with rest periods and earlier bedtime
- 3- Unable to maintain daily activities: able to perform only short episodes of activity
- 4- Confined to bed

Pain:

- 0- None
- 1- Minimal pain requiring no medication
- 2- Minimal pain controlled with over-the counter medication
- 3- Pain controlled with prescription medication and /or oral narcotics
- 4- Pain controlled with IV narcotics
- 5- Pain uncontrolled with IV narcotics

Pain Rating:

Patients subjective rating of degree of pain ranging from 0 (*no pain*) up to 10 (*severe pain*)

MUCOUS MEMBRANE ALTERATION

Esophagitis/Pharyngitis:

- 0- None
- 1- Dry sensation in throat and/or mild discomfort
- 2- Moderate pain requiring medication and soft diet
- 3- Severe pain requiring oral narcotics: unable to swallow soft foods
- 4- Severe pain requiring IV narcotics: chokes when tries to swallow water

SKIN INTEGRITY

Drainage:

- 0- None
- 1- Small to moderate amount of clear serous fluid: no odor noted
- 2- Moderate to large amount of serous fluid: no odor present
- 3- Moderate to large amount of serosanguineous fluid.
- 4- Moderate to large amount of seropurulent fluid: foul odor present

Integrity:

- 0- No changes noted
- 1- Faint or dull erythema: follicular reaction: itching
- 2- Bright erythema: tender to touch
- 3- Dry desquamation with or without erythema
- 4- Small to moderate amount of wet desquamation
- 5- Confluent moist desquamation: edema
- 6- Ulceration, hemorrhage or necrosis

VENTILATION ALTERATION

Cough:

- 0- None
- 1- Occasional non-productive (*dry*) cough
- 2- Persistent non-productive (*dry*) cough
- 3- Persistent dry or productive cough requiring over the counter antitussive agents
- 4- Persistent cough requiring narcotic antitussive agents
- 5- Severe dry or productive cough unresponsive to narcotic antitussive agents
- 6- Severe respiratory insufficiency requiring continuous oxygen therapy

Shortness of Breath:

- 0- None
- 1- Mild dyspnea with exertion
- 2- Dyspnea with minimal effort but not at rest
- 3- Dyspnea at rest: intermittent oxygen and/or steroid required
- 4- Severe respiratory insufficiency requiring continuous oxygen therapy

APPENDIX IV

PATIENT INSTRUCTIONS FOR SKIN CARE STUDY

BIAFINE® APPLICATION

BIAFINE®

Radiodermatitis emulsion, for topical application only

A. Product Description

Biafine® is a water-based wound dressing emulsion formulation which helps in the healing process of dermal wounds. When applied properly to a wound, Biafine® provides an optimum moist environment for the healing process, assists in the cleansing of the wound, and isolates the wound from bacterial exposure.

B. Indication for Use:

Biafine® is indicated for use in:

- Minor abrasions
- Superficial wounds
- Full thickness wounds, pressure sores, and dermal ulcers including lower leg ulcers
- 1st and 2nd degree burns, including sunburns
- Radiation therapy-induced skin reactions
- Dermal donor and graft sites

C. Ingredients:

Biafine® consists of purified water, liquid paraffin, glycol monostearate, stearic acid, propylene glycol, paraffin wax, squalene, avocado oil, trolamine sodium alginate, cetyl palmitate, methylparaben, sorbic acid, propyl paraben, fragrance.

D. Contraindications:

A known allergy to one of the ingredients in Biafine®.

E. Warnings:

In radiation therapy-induced skin reactions and/or in conjunction with ongoing radiation therapy do not apply Biafine® to the radiation treatment area less than 4 hours prior to a radiation treatment. Biafine® should be applied immediately following radiation sessions (*See Instructions for Use*).

Do not apply Biafine® to dermal grafts until after the graft has successfully taken.

F. Instructions for Use for Radiation Therapy Patients:

Apply a generous amount of Biafine® to the treatment area, gently massaging the Biafine® until it is completely absorbed. A white waxy residue may remain. Begin application after your first radiation treatment then two more times that day. Continue for two weeks after your treatment course is completed. Apply Biafine® three times each day (*seven days a week*) but not less than four hours before radiation therapy.

APPENDIX IV (continued)

PATIENT INSTRUCTIONS FOR SKIN CARE STUDY

BIAFINE® APPLICATION

G. Precautions and Observations:

1. For the treatment of any dermal wound, consult a physician.
2. Biafine® is non-toxic, however, it is for external use only and should not be ingested or taken internally.
3. Biafine does not contain a sun screen and should not be used prior to or during extensive exposure to the sun.
4. Do not use Biafine® in a bleeding wound until the bleeding has stopped.
5. The use of Biafine® on skin rashes due to allergies has not been studied sufficiently and is therefore not recommended.
6. Following the application of Biafine®, a temporary tingling sensation may occur (*for 10 - 15 minutes*) which is due to the stimulation of circulation at the wound site.
7. If signs of infection are present, appropriate antibiotic treatment should be started. Use of Biafine® can be continued during the antibiotic therapy
8. If your condition does not improve within 10 days, see your physician immediately.
9. Keep this and all medications out of the reach of children.

H. How Supplied:

Biafine® Radiodermatitis Emulsion for local application is available in 1.5 oz. (*42.0g*) and 0.66 oz (*18.6g*) lined tubes.

I. Manufactured For: (4/17/98)

Médix Pharmaceuticals, Americas, Inc.
6301 Ivy Lane
Suite 5100
Green Belt, MD 20770

J. Manufactured By:

Laboratoire Medix, S.A.
18, rue Saint-Mathieu 78550
Houdan, France

APPENDIX V

PATIENT INSTRUCTIONS FOR SKIN CARE STUDY

INSTITUTIONAL PREFERENCE

Product Name: _____ (*institution to fill in*)

Product Ingredients: (*institution to fill in*)

Contraindications: (*institution to fill in*)

Instructions for Use: (*institution to fill in*)

To the Patient:

Begin applying after your first radiation treatment. Product should be applied three times a day, seven days a week. **Do not apply product less than 4 hours before your daily radiation treatment.** Application of the product will continue for 2 weeks following your last radiation treatment.

(4/17/98)

APPENDIX VI

PRODUCT LOG

RTOG 97-13

Product: _____

Unit Size: _____

Date	9713 Case#	Patient's Initials	Quantity Dispensed or Received	Balance Forward	Lot #	Expiration Date	Recorder's Initials
1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							
11.							
12.							
13.							
14.							
15.							
16.							
17.							
18.							
19.							
20.							

(4/17/98)

APPENDIX VII

**STUDY PRODUCT SHIPPING FORM
RTOG 97-13**

Biafine (*and other institution-specified product*) 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 # _____

Indicate if you would like either of the following shipped:

Fruit of the Earth \emptyset *Aloe Vera Gel* and/or *CVS* \emptyset *Aloe Vera Gel*

Send Completed Form to:

*RTOG Headquarters
1101 Market Street
Philadelphia, PA 19107*

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

RTOG Headquarters Approval _____

Date: _____

(4/17/98)