

MEPILEX LITE

The Effect of Mepilex Lite Dressings on Acute Radiation-Induced Skin Reactions in Women Receiving Post-Mastectomy Irradiation

Dean Barrie Paterson

2011/2012

A thesis submitted for the degree of
Bachelor of Radiation Therapy with Honours
at the University of Otago, Dunedin, New Zealand

ABSTRACT

Acute radiation-induced skin reactions are a common side effect of breast radiation therapy. Reactions range from erythema, through dry desquamation to moist desquamation and can be a source of significant pain, discomfort and psychological distress, sometimes resulting in a treatment break. There is no standard method for the prophylaxis or management of these reactions. Practice is often based on historical or anecdotal evidence and considerable variation in skin care practices exist.

The aim of this trial was to investigate whether Mepilex Lite dressings are superior to standard care in reducing the extent of acute radiation-induced skin reactions in patients receiving treatment for breast cancer post-mastectomy. Mepilex Lite (Mölnlycke Health Care AB, Göteborg, Sweden) is a thin, self-adhering, absorbent, soft silicone dressing designed for the management of wounds and burns. It was hypothesised that Mepilex Lite would reduce reactions by protecting the irradiated skin against mechanical damage caused by friction and abrasion from clothing or adjacent tissue.

A multicentre, open-label, randomised, intra-individual comparison of 80 patients is being conducted. This thesis analyses a subset of 10 patients recruited at the Wellington Blood and Cancer Centre. At the first sign of erythema, the erythematous patch was divided into two equal halves; one half was covered in Mepilex Lite, the other treated with aqueous cream. In the event of moist desquamation, Mepilex Lite continued over the intervention patch and the department's standard dressing was used as the control. The Modified Radiation-Induced Skin Reaction Assessment Scale (RISRAS) was used to assess the outward signs (researcher component) and subjective symptoms (patient component) of the skin reaction three times a week during radiation therapy and once a week post-treatment until the reaction resolved. Patients also filled out an exit questionnaire on different aspects of the trial and the skin care agents.

Mepilex Lite dressings produced a significant decrease in the peak ($p=0.019$) and average ($p=0.031$) patient component of the RISRAS. This aligned with reports from the exit questionnaire. An anecdotal reduction in redness was supported by lower average ($p=0.012$) erythema RISRAS scores under the Mepilex Lite dressings. However, the decrease in peak erythema score and total researcher scores did not reach statistical significance in this small cohort. The impact of Mepilex Lite on moist desquamation could not be assessed in this small cohort due to the low incidence of moist desquamation in the study patches.

The results suggest that regardless of whether Mepilex Lite dressings reduce the visible signs of radiation-induced skin reactions in the final analysis of all 80 patients, its use may be justified based on the symptomatic relief it appears to provide in this small cohort.

ACKNOWLEDGEMENTS

It is a pleasure to thank the many people who made this trial and thesis possible.

First, I wish to thank all of the patients who committed their time and energy to participate in this study. I appreciate all of the feedback you provided and enjoyed spending time with you. Without you, none of this would have been possible. I hope you found the experience worthwhile and I wish you all the best for the future.

Thank you to all the staff at the Wellington Blood and Cancer Centre for your patience and support. I am grateful to the Consultants (Dr Carol Johnson, Dr Jamie Evans, Dr Neil Wilson and Dr Anna Nicholson) for supporting radiation therapist led research and introducing the trial to their patients. Thank you to Jennifer de Ridder and Sue Alexander for allowing me to combine the role of radiation therapist and research assistant. Your flexibility during this time has been very much appreciated. I am indebted to Jenni Reeves and Ruth Wickens for stepping into the role of research assistant when I was unavailable. Your assistance and advice has been invaluable.

I offer my sincerest gratitude to my supervisor Dr Ptries Herst for her enthusiasm, energy, encouragement and effort. Thank you for getting this project started and giving me this opportunity. Your dedication to this project has been greatly valued. I don't know how you managed to promptly reply to the hundreds of emails I sent you at all hours of the day and night. At times I would have been lost without you.

I am incredibly grateful to those who provided financial assistance towards the trial or my course fees. This includes:

- The Radiation Therapy Continuing Professional Development Fund
- The Cancer Society of New Zealand Wellington Division
- The Rouse Education Trust
- The University of Otago Research Fund
- The New Zealand Breast Cancer Foundation Post-graduate Radiation Therapy Scholarship

Lastly, I wish to thank Mölnlycke Health Care for providing all of the Mepilex Lite dressings free of charge; without your generous donation this trial would not have been feasible.

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1. INTRODUCTION

Breast cancer is the most common malignancy in New Zealand women [1]. Local radiation therapy is often indicated after breast conserving surgery or mastectomy to reduce the risk of local recurrence [2]. Ionising radiation causes damage to both healthy and malignant cells. External beam radiation therapy must pass through the skin to reach the target tissue. Therefore, acute radiation-induced skin reactions are an inevitable consequence of radiation therapy and occur in up to 95% of patients receiving treatment for breast cancer [3, 4]. Acute skin reactions range from erythema, through dry desquamation to moist desquamation and can be a source of significant pain, discomfort and psychological distress. In particular, moist desquamation poses the risk of infection and can result in treatment breaks, which can compromise patient outcomes [4].

There is a paucity of empirical evidence supporting the use of any particular topical agent or skin care regime for managing acute radiation-induced skin reactions [5]. As a result, considerable variations in skin care practices exist between radiation therapy departments and practice is often based on historical or anecdotal evidence. A survey by Kumar et al. [6] found that 50% of radiation therapy departments in Australasia based their skin care policy on anecdotal evidence. This highlights the need for a move towards evidence based skin care, which can only develop from well-designed clinical research.

Post-mastectomy irradiation is an ideal test bed for the comparison of topical interventions for the prevention and management of radiation skin toxicity [7]. The post-mastectomy chest wall provides a uniform surface that receives a relatively homogenous dose, compared with other sites where skin reactions are common. A number of authors [3, 7, 8] have suggested that physical protection against mechanical damage is one factor that promotes the repair of sub-lethal, acute radiation-induced skin damage. Mepilex Lite (Mölnlycke Health Care AB, Göteborg, Sweden) is a thin, self-adhering, absorbent, soft silicone dressing. We hypothesise that Mepilex Lite dressings will protect irradiated skin against mechanical damage caused by friction and abrasion against clothing or adjacent tissue, lessening the severity of acute radiation-induced skin reactions.

A multicentre, open-label, randomised, intra-individual comparison of Mepilex Lite dressings versus standard care during post-mastectomy irradiation in New Zealand is currently being conducted. This thesis reports the results of the first 10 patients available for analysis at the Wellington Blood and Cancer Centre (WBCC).

1.1. *Presentation of Acute Radiation-Induced Skin Reactions*

The term “acute radiation-induced skin reactions” is used to describe the spectrum of acute signs and subjective symptoms of skin damage that can result from therapeutic radiation therapy [9]. As the radiation beam must pass through skin to reach the target tissue, skin reactions are an inevitable and unavoidable consequence of external beam radiation therapy. Acute or early skin reactions are reversible and occur within 90 days of the initiation of treatment [10, 11], with the peak reaction usually occurring between five and 10 days post-treatment [12].

The true incidence of acute radiation-induced skin reactions is difficult to assess due to poor prospective and systematic recording of skin toxicity outside of clinical trials [4]. Some authors report that skin changes may be experienced by up to 95% of patients receiving radiation treatment to the breast, although the severity of these reactions is highly dependent on a number of treatment and patient related factors [4, 13]. The introduction of modern mega-voltage treatment machines, with skin-sparing capabilities, has ameliorated but not eliminated skin toxicities [10].

Acute radiation-induced skin reactions occur in varying degrees of severity and are dose dependant. Skin reactions progress from erythema, through dry desquamation to moist desquamation and in very extreme cases necrosis [14]. A range of reactions can be present in the treatment fields at any one time.

1.1.1. Erythema

Erythema (Greek for “redness”) is the most common radiation-induced skin reaction (Figure 1.1). It is characterised by increasingly reddened skin which often becomes oedematous and hot [12]. Skin colour ranges from a dusky pink (faint erythema) through to deep red/purple (bright erythema) and is associated with feelings of itchiness, tingling, tenderness, discomfort and a burning sensation [9]. Erythema may have a rash-like appearance and is often described as resembling sunburn [3, 13].

Transient faint erythema can occur within hours of the first treatment fraction. It is often unrecognised and fades within days [4, 10, 15]. A subsequent phase of persistent erythema usually develops during the second or third week of treatment, which equates to a dose of between 20 and 30 gray (Gy), based on a standard fractionation regime [10, 14, 16, 17]. Hyperpigmentation or tanning of the skin, caused by increased melanin production, can also occur in the same time frame as erythema [15].

1.1.2. Dry Desquamation

Progression to dry desquamation (Figure 1.1) involves the red skin becoming dry and scaly, with flaking and peeling of the epidermis [14]. Dry desquamation typically manifests three to six weeks after treatment commences at doses between 40 and 60Gy [2, 18].



Figure 1.1 Area of untreated skin compared to irradiated skin showing Erythema and Dry Desquamation.

The area to the left of the black line is normal, unirradiated skin. The area to the right of the black line is erythematous skin with dry desquamation (arrow).

1.1.3. Moist Desquamation

Moist desquamation (Figure 1.2) can follow soon after dry desquamation. This involves the skin surface peeling or blistering to expose the dermis. The wound is moist, tender, red and leaks serous fluid and exudate [13]. Re-epithelisation typically occurs by the third week post-treatment, although it can take up to six weeks to fully resolve [18, 19]

Moist desquamation is the most clinically relevant acute skin reaction. Affected skin is at risk of infection and can prompt the suspension or early completion of radiation treatment, thereby compromising treatment outcome [10, 20, 21]. In addition, moist desquamation can have a significant effect on wellbeing by limiting the patients' daily activities and compromising their quality of life.

Wells and MacBride [4] reviewed a number of trials and reported that moist desquamation is likely to affect 10-15% of patients receiving radiation treatment. Certain treatment sites and regimes are

more likely to result in this reaction. Graham et al. [7] reported that 46% of women receiving radiation therapy to the post-mastectomy chest wall experienced moist desquamation in the control arm of their trial which compared Cavilon No-Sting Barrier Film to sorbolene cream. Moist desquamation is therefore a significant issue for this cohort of patients.

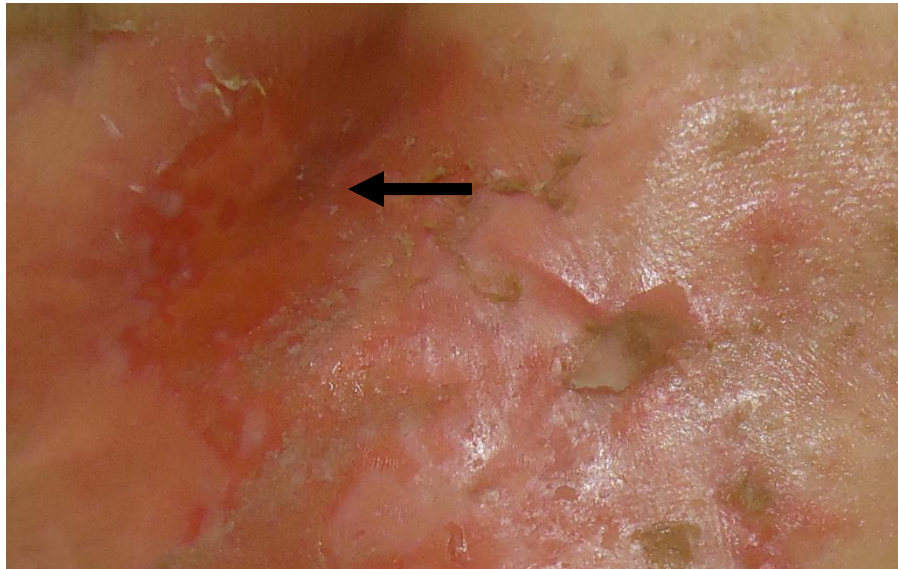


Figure 1.2 Area of irradiated skin showing moist desquamation (arrow).

1.2. Pathophysiology of Acute Radiation-Induced Skin Reactions

1.2.1. Skin Structure

The skin consists of the epidermis and the dermis. The epidermis forms the superficial, protective layer of the skin. It is 30-300 micrometres thick and is composed of a proliferating basal layer containing stem cells which is covered by multiple layers of non-dividing, differentiating cells which migrate to the surface and become keratinised. Newly differentiated cells continuously replace the outer cells of the keratinised layer as they are shed or detached. The entire layer is replaced approximately every four weeks [13, 14, 16]. Melanocytes and Langerhans cells are also found scattered in the epidermis. Melanocytes produce melanin pigment to protect the basal layer against damage from ultra-violet (UV) light [22]. Langerhans cells are dendritic cells which are mobile in the epidermis and dermis; they check these tissues for the presence of foreign materials as part of the body's immune system.

Deep to the epidermis is the dermis (1-3mm thick). This layer of dense connective tissue contains support structures including blood vessels, nerves, glands and hair follicles [22, 23]. Acute radiation-induced skin reactions result from a combination of inflammatory effects and direct injury to the cells of the epidermis and dermis.

1.2.2. Pathophysiology of Erythema

Erythema is an inflammatory response caused by increased blood flow beneath the epidermis [15, 19]. Ionising radiation damages germinal cells, which release histamine into underlying tissues. This results in capillary dilation, increased vascular permeability and dermal oedema [14, 15].

1.2.3. Pathophysiology of Desquamation

Desquamation occurs following the failure of the skin's cell renewal system. The basal cells of the epidermis react very quickly to radiation [4]. Fractionated radiation therapy repeatedly damages the mitotic ability of stem cells in the basal layer, resulting in cell cycle blockade [4, 13]. The injured basal cells continue their migration to the skin surface, become keratinised and are shed as part of the normal process. If repopulation of the basal layer occurs from surviving stem cells prior to desquamation, the skin surface can become dry and flaking (dry desquamation) [14]. Further dryness and hair loss are the consequence of damage to the glands and hair follicles [10].

Moist desquamation occurs when new cell proliferation is inadequate or nonexistent due to the complete lack of mitosis of stem cells in the basal layer. In the absence of new cells forming, damaged tissue is not replaced, compromising the integrity of the epidermis and exposing the dermis [15, 23].

1.2.4. Repair of Radiation-Induced Desquamation

Repair and regeneration of new skin is triggered by a homeostatic stimulus or feedback mechanism, usually beginning one week post-treatment [13, 19]. Skin may regrow as small islands within the irradiated field from surviving stem cells. If no stem cells remain, new cells are produced from stem cells that migrate from the periphery of the wound or treatment field [19].

Although the skin may begin to appear normal, it never completely recovers. The newly formed epidermis is thinner and less resistant to injury [16]. According to Moss et al. [15], every acute skin reaction is followed by some form of permanent or late change, though it may be slight and clinically insignificant. Sebaceous glands do not usually recover, however sweat gland function typically resumes after two weeks [19].

Chronic or late radiation-induced skin reactions can occur months or years after treatment. Late reactions include hypopigmentation, telangiectasia, fibrosis and secondary malignancies [16]. These reactions are not the focus of this thesis and will not be explored further here.

1.3. Factors Affecting the Severity of Radiation-Induced Skin Reactions

A number of factors are thought to increase the likelihood that a patient will develop a severe acute radiation-induced skin reaction. Although it remains difficult to predict exactly which patients will develop a severe reaction, these factors can guide healthcare professionals in providing an individualised approach to patient education and skin care. Even with identical treatment regimens, considerable variation in the severity of reactions is observed between patients.

Porock et al. [24] developed a conceptual framework, based on knowledge of radiobiology and wound management, which organises these factors into three categories: radiation construct, genetic construct and personal construct. This framework has been adopted in this thesis and supplemented with further research into factors that may affect the severity of acute skin reactions in patients receiving radiation treatment for breast cancer (Table 1.1).

Table 1.1 Factors Affecting Radiation-Induced Skin Reactions

Radiation Construct	Genetic Construct	Personal Construct
Dose/Fractionation	History of cancer	Age
Volume	Genetic co-morbidity	Weight
Site	Cancer-prone family	Tumour size
Technique	Hereditary cancer	Co-morbidity
Energy	Skin colour	Chemotherapy
Bolus		Nutrition
		Smoking
		Infection
		Seroma aspiration
		Ultraviolet exposure

Adapted from Porock et al. [24]

1.3.1. Radiation Construct

Dose and Fractionation

Radiation reactions are dose-dependent [4, 13]. A higher total dose results in increased single and double stranded DNA breaks and therefore a greater degree of cell damage [10]. Dose rate has also been shown to affect the degree of erythematous change in clinical trials [25]. According to Sitton et al. [23], dose per fraction has a greater effect on late tissue complications than on acute complications. All patients at the WBCC are treated with a 600cGy/min dose rate and the majority of post-mastectomy patients receive 50Gy in 25 fractions over five weeks.

Treatment Volume

Increased treatment volume has been linked to more severe reactions [13, 23]. Porock [26] hypothesises that this relationship may be due to the fact that a small area of skin loss is easier to heal. It is also likely that there is increased discomfort and a greater variation in skin dose over a larger volume [26].

Site/Location

This factor has been adapted to relate directly to breast treatments. In a paper describing the incidence of acute skin reactions in breast patients, Porock and Kristjanson [3] identify the axilla as displaying the highest frequency of moist desquamation, followed by the infra-mammary fold. These locations are more prone to friction, warmth and moisture [23] than other areas of the breast. As the patients in the current trial have had a mastectomy, the infra-mammary fold is not an issue.

Bolus

Bolus is a tissue equivalent material used to increase dose to the skin or tissue immediately deep to the skin [4]. Use of bolus can therefore significantly increase the severity or likelihood of an acute skin reaction. Patients at the WBCC have three millimetres of bolus applied to the post-mastectomy chest-wall as per department protocol. This maximises dose to the skin and target tissue immediately deep to the skin, where there is risk of local recurrence.

Energy

The treatment energy and type of radiation is directly related to the dose absorbed by the skin. The orthovoltage units (200-300kVp) that were commonly used for breast treatments until the 1950's deposited the dose maximum on the skin surface [23]. Modern mega-voltage linear accelerators are significantly more skin sparing and have a depth of maximum dose of approximately 1.5cm for 6MV

and 3.5cm for 18MV. Electron beam therapy is often used for tumour bed boosts and is occasionally used to treat the post-mastectomy chest wall. Electrons have a rapid build-up region near the skin surface and more than 80% of the dose is absorbed on the skin, often resulting in more severe skin reactions [2, 23].

Treatment Technique

The standard tangential beam arrangement commonly used to treat the breast or chest wall, diminishes the skin sparing effect of mega-voltage radiation [23, 26]. Tangential beams “glance” the skin surface resulting in a higher dose being delivered to the skin than when beams enter perpendicularly to the body. Variations of this technique are employed worldwide and it is the method employed to deliver breast and chest wall irradiation at the WBCC (Figure 1.3). A recent randomised controlled trial (RCT) conducted by Pignol et al. [27] found that intensity-modulated radiation therapy (IMRT) significantly reduced the occurrence of moist desquamation, compared to a standard tangential beam arrangement, in women receiving radiation treatment to the breast. IMRT is an advanced treatment technique that involves computer controlled modulation of the beam intensity across the target area. The radiation beam is divided into multiple “beamlets”, each with its own intensity (Figure 1.3). IMRT reduces skin toxicity by creating a more homogenous dose distribution and reducing dose “hot spots” [27].

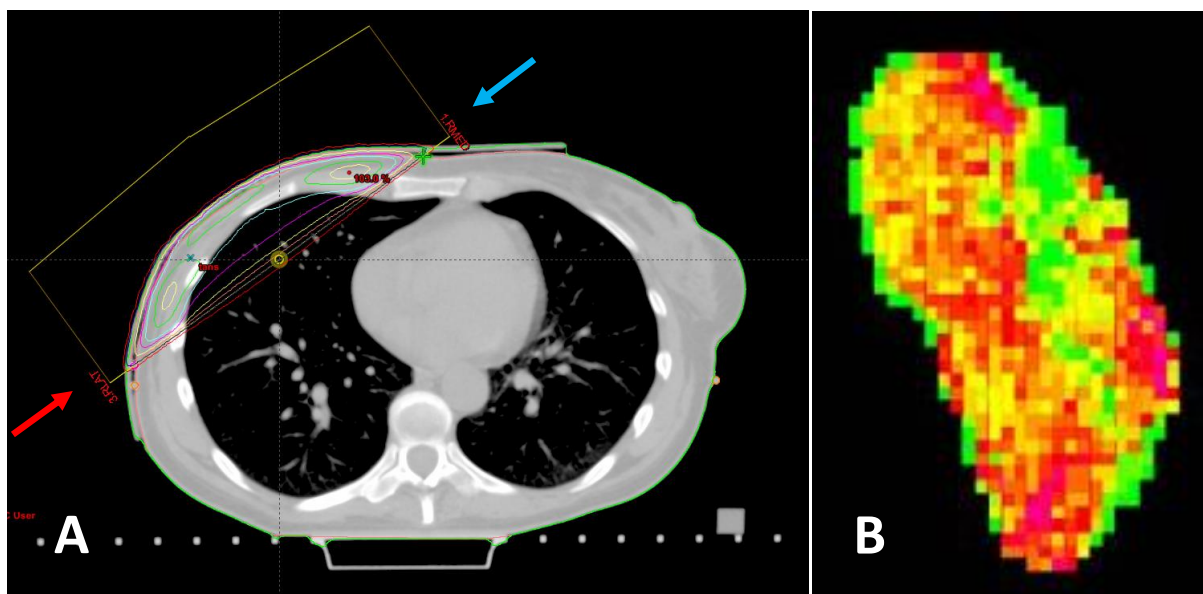


Figure 1.3 Standard tangential beam arrangement (A) and beams eye view profile of an IMRT beam (B)

A. A medial field (blue arrow) and an opposing lateral field (red arrow) being delivered at a tangent to the patient's chest wall. The purpose of this technique is to maximise coverage of the breast/chest wall and minimise dose to underlying structures, such as the heart and lung. The posterior halves of the beams are blocked to reduce radiation scatter to these tissues. B. Each “beamlet” is represented by a small square denoting either high (red), moderate (yellow) or low (green) intensity.

1.3.2. Genetic Construct

Some individuals have a predisposition to increased radiosensitivity and impaired wound healing. A literature review by Andreassen [28] identifies a number of complex genetic factors that may influence the intrinsic radiosensitivity of an individual. These include possessing variants of genes related to: DNA repair, inflammatory cytokines, endogenous antioxidant enzymes, as well as general metabolism and homeostasis. Other genetic factors, identifiable by the practicing clinician, are explored below.

Skin Colour

Anecdotal evidence suggests that individuals with pale or fair skin experience more severe radiation-induced skin reactions than those with darker skin; similar to the tendency of lighter skin to get sun burnt more easily than darker skin. A lack of empirical data exists to support this claim [26]. In fact, Ryan et al. [29] found that African-American women reported more severe skin reactions than Caucasian women post-radiation therapy to the breast. It is possible that women of different ethnicities perceive or evaluate their skin reactions differently, rather than there being any quantifiable differences in the degree of erythema or desquamation [30]. In addition, early reactions may be more difficult to see on darker skin and are therefore not managed appropriately at an early stage, resulting in more severe reactions at a later stage.

History of Skin Cancer/Ultra-violet (UV) Exposure

Porock et al. [24] categorise a “history of skin cancer” as a genetic factor. This group found that a history of skin cancer correlated with a greater than tenfold risk of developing a severe skin reaction over the sternum in patients treated for breast cancer. Porock et al. [24] speculate that these patients could demonstrate a greater sensitivity to UV radiation and therefore may have a greater propensity to increased radiosensitivity.

An alternative view is that a history of skin cancer is a conservative estimate of previous UV exposure and sun damage [24]. Perhaps this factor would be better classified combined with UV exposure under personal construct. Porock et al. [24] also hypothesised that UV radiation thins the epidermis or impairs the inflammatory phase of healing, leading to more severe acute radiation-induced skin reactions.

Genetic Co-morbidity

A number of genetic diseases have been linked to increased skin radiosensitivity. The most documented of these is ataxia telangiectasia mutation (ATM), which is a rare autosomal-recessive disorder [10]. The ATM gene is involved in DNA repair. As ionising radiation produces DNA damage, patients with reduced capability for DNA repair are at increased risk of severe skin reactions and other radiation-induced side effects [10]. Other genetic disorders, such as Fanconi's anaemia, Bloom syndrome and Gardner's syndrome, have been linked to an increased frequency of chromatid breaks after radiation therapy which results in increased radiosensitivity [10].

Cancer-prone Family and Hereditary Cancer

Carriers of the hereditary BRCA1 or BRCA2 mutations may have an increased risk of normal tissue damage, as well as the well-documented increased risk of breast and ovarian cancer development [28]. These genes are involved in the sensing and repair of DNA damage. An *in vitro* experiment conducted by Buchholz et al. [31] demonstrated that fibroblasts and lymphocytes, heterozygous for BRCA1 or BRCA2 mutation, were more radiosensitive compared with cells from individuals without these mutations.

1.3.3. Personal Construct

Personal factors are factors that are considered unique for each individual. These factors have been studied the least and there is little empirical evidence to indicate the extent of their influence on acute radiation-induced skin reactions [24].

Age

Controversy exists regarding the effect of age on radiation-induced skin reactions. Traditionally, older age has been thought of as a significant predictor of increased skin reactions [26]. The rate of mitosis in the basal layer of the epidermis decreases with age. This results in thinning of the epidermis, increased re-epithelisation times and an increased risk of infection. Ageing cells also cause dermal atrophy through loss of collagen and a diminishing capillary network [26].

In contrast to this view, Porock et al. [24] found that increasing age correlated with a decreased risk of an acute radiation-induced skin reaction over the sternum in women treated for breast cancer. Younger patients are more likely to have chemotherapy, which has also been linked to an increased skin reaction. Although the authors cannot rule chemotherapy out as a potential confounding factor,

they also provide the alternative hypothesis that the reduced rate of epidermal cell division in older patients may reduce the impact of ionising radiation on their skin.

Weight/Breast Size

Increased breast size and weight correlates with increased skin reactions in the axilla and inframammary fold of patients with breast cancer [24]. Larger patients require a higher skin dose to ensure adequate coverage of deeper target tissues and reduced vascularity in adipose tissue may compromise healing. Furthermore, increased skin folds will produce more friction, particularly in the axilla and inframammary fold [24]. The results of a retrospective audit in Australia support this finding [32].

Smoking

Carbon monoxide and nicotine in cigarette smoke limits the oxygen carrying ability of haemoglobin and causes cutaneous vasoconstriction. This results in reduced healing and re-epithelisation rates [24, 26].

Nutrition

Good nutrition is essential for the repair of radiation-induced skin damage. Malnourished patients lack essential nutrients, such as nitrogen. As a result, healing times are decreased and tissue repair is delayed [23, 26, 33, 34].

Seroma Aspiration

Congestion occurs due to damaged lymphatics and the inflammatory response to radiation causes an increase in breast lymphoedema, necessitating seroma aspiration. Porock et al. [24] observed that patients who required seroma aspiration were more likely to experience a severe skin reaction in the breast and axilla.

Tumour size

Porock et al. [24] also identified tumour size as a predictor of skin reactions. Women with larger breast tumours experienced worst reactions in the upper breast. A possible explanation is that larger tumours required more extensive surgery, resulting in more trauma and oedema to surrounding tissue.

Co-morbidity

A number of non-genetic diseases have been reported as predisposing individuals to increased skin reactions, however little empirical evidence exists to support these claims [26]. These co-morbidities include pre-existing connective tissue or autoimmune conditions that may retard the healing process, such as scleroderma, rheumatoid arthritis, allergies and systemic lupus erythematosus [10, 26]. Turesson et al. [34] reported that peak erythema scores, measured by reflectance spectroscopy, were dependant on systolic blood pressure. A higher blood pressure gave a more pronounced peak erythema reading. Diabetes is also thought to affect wound healing time [33], most likely due to its effects on the vascular system.

Chemotherapy

A number of cytotoxic chemotherapy agents commonly used in the treatment of breast cancer have been linked to increased skin toxicity (e.g. adriamycin, docetaxel, paclitaxel) [4, 10, 26]. The effect of these drugs is dependent on both the schedule and dose at which they are given. In their retrospective audit, Back et al. [32] found that CMF chemotherapy (cyclophosphamide, methotrexate and 5-fluorouracil) was statistically significantly related to increased moist desquamation in women receiving radiation treatment to the breast. Additionally, there was a trend towards the reaction being worst when the chemotherapy was delivered concurrently (rather than sequentially), although this did not reach statistical significance.

1.4. *Impact on Quality of Life*

Acute radiation-induced skin reactions can be very distressing for women receiving treatment to the breast. From a patient's perspective, skin toxicity is rarely seen as only a physical experience and the reaction often has a lasting negative impact on quality of life and emotional well-being [35]. Even prior to treatment, many women suffer from fear and anxiety at the prospect of experiencing a severe, potentially debilitating radiation-induced skin reaction. In one study, 69.1% of women receiving treatment for breast cancer feared radiation-induced side-effects, although this was not specific to skin toxicity [36]. These initial fears were often worse than the actual experience, which indicates the need for health professionals to provide reassurance and information about managing these reactions prior to treatment [37]. There has been a paucity of research focussing specifically on the experience of skin toxicity and its impact on quality of life during radiation therapy for breast cancer. A recent qualitative study by Schnur et al. [30], found that skin toxicity affected multiple dimensions of quality of life. These dimensions included: physical effects, body image disturbance, emotional reactions, day-to-day functioning and satisfaction with radiation treatment.

Schnur et al. [30] reported that acute radiation-induced skin reactions caused significant physical discomfort in patients with breast cancer. Feelings of pain, burning, itchiness, pins and needles and heaviness were described by the participants. Some women also commented on how their skin texture changed and used descriptors such as: "peely, rougher, harder, leathery, warmer, tougher, patchy, bumpy, scaly, and like a lizard" [30: p.263]. An important finding was that several women specifically mentioned that their reaction did not feel like sunburn, as it is often described by health professionals, or that it was much worse than sunburn. This has important implications for health professionals who are informing and educating patients about skin care prior to treatment.

The cosmetic effects of acute skin reactions may lead to anxiety and body image dissatisfaction. In one cohort of women, almost 40% feared radiotherapy-associated changes to breast appearance [36]. Similarly, many women in the study by Schnur et al. [30] were distressed by the colour and texture changes of their treated breast and the difference this created between their breasts. Some women displayed anxiety at having to explain these differences to others and thought of these changes as a "signal of unhealthiness and illness and sickness" [30:p.263]. Other emotional responses to skin changes included fear of treatment being stopped due to severe reactions as well as feelings of being irritable and increased impatience.

Many women make changes to how they live their day-to-day lives in order to deal with acute radiation-induced skin reactions. Wengstrom et al. [38] found that physical functioning decreased as radiation treatment progressed in a sample of women with breast cancer. The impact of increasingly severe acute skin reactions provides one explanation for this. During treatment, the skin often becomes too sensitive to wear a bra or prosthetic breast. Both Halkett et al. [37] and Schnur et al. [30] found this to be a significant cause of anxiety, especially for larger women or for women celebrating special occasions. Additionally, sleep deprivation can occur related to burning and the constant need to reposition due to discomfort [30]. Many radiation departments advise patients not to use a deodorant of any kind during treatment to the breast as it is thought to increase skin toxicity in the axilla [39]. This may lead to concerns about body odour and personal hygiene which can negatively impact social functioning during treatment [30].

Finally, patient satisfaction with radiation therapy may be affected by skin toxicity. The experience of skin toxicity can cause patients to consider quitting treatment or refusing further treatment in the future [30]. Furthermore, some individuals believe that after radiation treatment they may never be healthy again due to skin changes [35]. It is interesting to note that some patients experience skin toxicity in a positive way and interpret it as a sign the treatment is working or being performed correctly as demonstrated by this quote: "I know they're aiming right. It's a check." [35:p.672].

1.5. Skin Care

1.5.1. Lack of Empirical Evidence

There is a paucity of empirical evidence supporting the use of any particular topical agent or skin care regime during radiation therapy. As a result, skin care practice is often based on anecdotal evidence and practices that have evolved historically [6, 8, 12, 13, 40, 41]. These practices are often based on individual opinion or consensus and as a result considerable variation in practices exist.

In a recent survey, Kumar et al. [6] found that 50% of responding departments in Australia and New Zealand based their skin care policy on anecdotal evidence. This situation is not limited to Australasia. Other authors have demonstrated that skin care practices vary between institutions and in some cases there is substantial intra-institution variability [12, 39, 40]. This is especially true for practice concerning washing, deodorant use and applying topical creams/lotions on irradiated skin. D’Haese et al. [12] studied the consensus of skin care practice amongst radiation therapy departments in Flanders, Belgium. Their survey consisted of 58 items/practices regarding the prophylaxis and management of acute radiation-induced skin reactions. Overall, only 33% of these items showed a large consensus between nurses, with the lowest consensus seen in the case of erythema and preventative advice. A survey of skin care practices in Canada by Bolderston [39] produced a similar result. An interesting finding of the Canadian study was that most departments were unable to provide a single skin care management approach as it was dependant on the preferences of the treating consultant. This is demonstrated particularly well by the responses: “Our written sheet has both cornstarch and moisturisers on it as different doctors recommend one or the other. The therapist then asterisks which one the particular patient has to use” (p.4) and “We would also have patients in the waiting room, with the same site and fractionation but very different skin care instructions and this isn’t good practice” (p.6). These inconsistencies in practice may be a source of stress for patients, undermine trust and potentially compromise the prevention and healing of acute radiation-induced skin reactions [42].

1.5.2. Skin Care Guidelines at the Wellington Blood and Cancer Centre

The WBCC provides patients with standardised guidelines designed to inform them on how to care for their skin during and immediately after radiation treatment to the breast or chest wall. This advice applies from the start of treatment until their reaction has healed:

Do

- Use a moisturiser such as aqueous cream or calendula cream on the treated area. Do this at least twice a day. Avoid using any other creams, lotions, cosmetics, perfumes etc on the area (including sunscreen).
- Use a mild soap e.g. Dove, Simple or baby soap
- Minimise friction in the area. You can do this by putting a silk scarf or cotton handkerchief between the skin and your bra.
- Maintain good personal hygiene. This is important, so please bath or shower regularly. Use a soft towel and pat the skin dry rather than rubbing it.

Do Not

- Do not use deodorants containing aluminium, alcohol or silver under the arm on the treated side.
- Do not shave, use wax or hair removal creams on the treated side. If necessary, shaving should only be done with an electric razor.
- Do not expose the treated area to direct sunlight (remember the neckline area, especially V necks).
- Do not apply any cream or deodorant of any description if the skin breaks. This may cause complications with infection.

WBCC [43]

This protocol is consistent with clinical practice guidelines published by a number of authors [4, 16, 41]. These general interventions and recommendations are focussed on promoting comfort, cleanliness, preventing further trauma and avoiding any substances that may increase the skin reaction [13]. Although aqueous cream has not been shown to be superior to no skin treatment [44]; the initial use of a plain, non-scented, lanolin-free, hydrophilic cream is thought to be helpful in preventing radiation skin reactions [4, 41]. Aqueous cream was designed as a soap substitute and contrary to common practice may not be appropriate as a leave-on emollient, due to the presence of sodium lauryl sulphate, which has recently been shown to cause irritation and damage to the skin barrier [40, 45]. Therefore, although this practice remains the current standard of care, it may be discouraged in future guidelines.

WBCC protocol advocates a low dose corticosteroid cream (hydrocortisone 1%) for pruritus and provides general principles for the care of moist desquamation [46, 47]. Areas of moist

desquamation are dressed with a hydrogel, such as Solosite (Smith & Nephew) and are covered with Cuticerin (Smith & Nephew), a non-adherent wound contact layer. This is covered with a Combine (Smith & Nephew) pad, which is an absorbent dressing that provides protection and padding. Dressings are held in place by a bra or are taped to skin outside the treatment fields [46, 47].

1.5.3. Prophylaxis of Acute Radiation-Induced Skin Reactions

Multiple studies have investigated the efficacy of topical agents for the prevention or prophylaxis of acute radiation-induced skin reactions. In 2006 the Cancer Care Ontario Supportive Care Guidelines Group (CCOSCGG) published a comprehensive systematic literature review [41] which aimed to determine the optimal skin care practice for patients receiving radiation treatment. This review included 28 comparative studies published prior to 2004, and concluded that there is insufficient evidence to support or refute the use of specific topical agents; although limited evidence suggested that calendula cream may reduce the incidence of moist desquamation. The CCOSCGG also recommended that gentle skin washing with a mild soap should be permitted and that personal hygiene practices should not be restricted [41]. A literature review by McQuestion [13] supported these claims.

This section provides an up-to-date overview of the literature published since the CCOSCGG review [41]. It is not intended as a comprehensive systematic review and only includes English language articles available from the University of Otago, which investigated topical agents for the prevention of acute radiation-induced skin reactions. To be classified as a prevention trial, use of the topical agent commenced prior to or at the start of radiation therapy. A total of 20 articles were identified and are summarised in Appendix A. There is a small degree of overlap with the CCOSCGG review as papers published in 2004 have been included. The majority of the studies reviewed utilised either the Radiation Therapy Oncology Group (RTOG) [48] or the National Cancer Institute Common Toxicity Criteria (NCI-CTC) [49] assessment scales for grading acute radiation-induced skin reactions (Appendix B).

Théberge et al. [50] and Bennett [51] conducted single-blinded RCTs which aimed to determine the effect of non-metallic deodorant use on the RTOG grade of acute skin toxicity in patients receiving radiation treatment to the breast or chest wall. In both trials, deodorant use was compared to no deodorant use. Traditionally, many practitioners have prohibited deodorant use due to fears it could create a bolus effect, contain chemicals that further irritate the skin or contain metallic particles which could produce scatter and increase radiation dose to the skin [41, 51].

These two trials had a calculated study power, which resulted in sample sizes of 84 [50] and 190 [51]. The sample size calculated by Théberge et al. [50] was most likely smaller due to the non-inferiority approach taken in their power calculation. Although smaller, the trial by Théberge et al. [50] had a number of methodological advantages over Bennett's trial [51]; such as, including a skin assessment post-radiation treatment, including patient rated assessments of subjective symptoms and stratifying the trial arms based on axillary irradiation and adjuvant chemotherapy. Skin assessments post-treatment are important as reactions typically reach their peak around two weeks after the completion of radiation therapy [43]. Both RCTs found no significant difference in the acute skin toxicity between groups who did and did not apply a deodorant during radiation treatment. The researchers [50, 51] concluded that non-metallic deodorants do not need to be restricted in this cohort of patients.

A further two RCTs [52, 53] investigated topical corticosteroids for the prevention of acute skin reactions in patients receiving radiation treatment for breast cancer. Shukla et al. [52] conducted an open-label comparison of beclomethasone spray to no skin treatment in the axilla of 60 patients. A statistically significant decrease in the incidence of moist desquamation was detected with use of the spray (13.33% vs. 36.66%; $p=0.0369$). This group used an in-house scale to grade skin toxicity; however, the scale was not reported in their publication. Another limitation of this trial was the lack of blinding, which could have been adapted into the trial design by using a placebo solution in an identical spray bottle. Omidvari et al. [53] also examined topical corticosteroid use. This group conducted a double-blinded RCT and detected a strong trend towards a lower mean RTOG grade in patients ($n=51$) applying topical betamethasone, compared to a vehicle emollient and no skin treatment. This trend almost reached statistical significance ($p=0.055$).

Neither of these trials included a measure of the patients' subjective symptoms or experience of their skin reaction and both included a no skin care arm. A no treatment arm could be considered unethical and would likely result in poor patient accrual in New Zealand. In addition, the treatment technology used (Cobalt unit [52] and 120kV superficial x-ray machine [53]) was significantly less skin sparing than the modern linear accelerators used in New Zealand. Nonetheless, anecdotal evidence suggests that low dose corticosteroids are beneficial in reducing pruritus and as such are commonly prescribed at the WBCC.

A third cluster of trials [54-56] investigated the effect of creams containing hyaluronic acid (HA) on the skin of patients' receiving radiation to the breast or chest wall. HA is a powerful moisturiser and a

major constituent of the extracellular matrix of the skin. It is thought to facilitate tissue repair by stimulating the migration of phagocytes and fibroblasts as well as stimulating endothelial cell proliferation [57]. All three trials reported a statistically significant decrease in skin toxicity in favour of the HA based cream. Two of these trials [54, 55] were double-blinded RCTs and compared a HA based cream to a vehicle emollient. The trial conducted by Primavera et al. [54] was an intra-individual comparison where each patient acts as their own control in order to reduce patient and treatment related confounding factors. Neither of these trials had a calculated study power and the sample sizes were relatively small ($n=20$ & 40). Leonardi et al. [55] reported that the HA based cream statistically significantly reduced the maximum severity of the NCI-CTC grade ($p<0.0001$), whereas Primavera et al. [54] only demonstrated a significant reduction in NCI-CTC grade at week five of treatment ($p=0.031$). In addition, Primavera et al. [54] employed a number of objective skin assessment techniques and showed a significant reduction in erythema using reflectance spectroscopy ($p=0.004$). No significant difference was found between groups in the patients' experience of pain or itching. A significant difference ($p=0.039$) was detected in self-reported burning sensation by Leonardi et al. [55].

The third trial [56] was a larger ($n=98$) observational study, which used historical controls for comparison. It is unclear which skin care regime the control patients used, and the study cream contained two other active ingredients (3% urea and polidocanol), which are likely to have influenced the results. Urea acts by retaining water in the stratum corneum and was added in an attempt to maintain the balance of humidity and flexibility of the skin. Polidocanol is an exothylated fatty alcohol with local anaesthetic properties [56]. Patients using the HA based cream followed an "intensive use" protocol and commenced applying the cream three weeks prior to radiation treatment. The researchers reported a statistically significant reduction in RTOG grade 2 skin toxicity (21.4% vs 40.8%; $p<0.001$) with the HA based cream as well as a significant increase in the proportion of patients who did not develop any skin toxicity (27.6% vs 15.5%; $p<0.05$). Although this group recorded patient reported symptoms on a visual analogue scale, these results were not reported.

Sucralfate cream was investigated by two groups [44, 58]. It was hypothesised that sucralfate cream would reduce the extent of skin reactions due to its ability to stimulate a number of growth factors and scavenge free radicals [58]. Wells et al. [44] conducted a large ($n=357$), double-blinded RCT comparing sucralfate cream to aqueous cream and no skin treatment in patients receiving radiation therapy to the breast, anorectal area or head and neck. Although this trial is reported as double-blinded, patients would be aware if they were on a skin treatment or no skin treatment arm. Analysis

was done on an intention to treat basis and inter-rater reliability tests were performed on the research assistants (although the results of this are not reported). The modified RTOG scale used is a good alternative to the standard RTOG scale, as it avoids pooling together different types of skin reactions. The researchers also used a reflectance spectrometer for quantitative evaluation of erythema and Likert scales to assess the subjective symptoms of the skin reactions experienced. Although it is an advantage to have a quantitative measure of skin toxicity, the relevance of the information is limited as it can only give information on the degree of redness. No meaningful reduction in acute skin toxicity was found for sucralfate cream. In addition, there was no significant difference in skin toxicity between patients using aqueous cream and those with no skin treatment. Despite this finding, a simple emollient, such as aqueous cream, is recommended by over 70% of radiation therapy departments in Australia and New Zealand [6].

Falkowski et al. [58] conducted a small (n=21), open-label, intra-individual comparison of sucralfate cream and no skin treatment in patients receiving radiation to the breast. For each patient, the sucralfate cream was applied over the whole breast except for a 5x5cm section in the upper-inner quadrant, which acted as a control. Unlike other intra-individual controlled trials, this trial lacked internal randomisation as to the location of the test agent on the patient's skin, which would have protected against the potential for the skin reaction to be systematically better/worse in a particular area. This trial also lacked skin assessments after the completion of radiation treatment and a measure of the patients' subjective symptoms. Similar to Wells et al. [44], no benefit for sucralfate cream was demonstrated in terms of RTOG grade skin toxicity or reflectance spectrometer reading.

Five trials investigated trolamine for the prophylaxis of acute radiation-induced skin reactions. In three of these trials trolamine was the intervention agent [59-61] and in two trials it was the control agent [62, 63]. Trolamine (Biafine) is an oil-in-water emulsion with anti-inflammatory properties. It is able to enhance wound healing by attracting macrophages and promoting the production of granulation tissue [61]. Only one [61] of these trials detected a statistically significant reduction in the RTOG grade of skin toxicity in favour of trolamine ($p<0.01$). This was a small (n=30), open-label, RCT that compared trolamine to usual supportive care (moisturiser optional) in patients receiving radiation treatment to the head and neck. No study power was calculated and the patients' subjective experience of their skin reaction was not considered.

A large (n=254), single-blinded RCT by Pommier et al. [62] compared trolamine to Calendula cream and detected significantly less ($p<0.001$) RTOG grade 2 toxicity in favour of the Calendula cream. In

addition, a multivariate analysis of the results identified a number of prognostic factors for the severity of radiation-induced skin reactions (increased body mass index and adjuvant chemotherapy). Double-blinding was not possible due to obvious differences between the two creams (smell, texture). As a result of this trial, Calendula cream is permitted for the prophylaxis and management of erythema at the WBCC [43]. The remaining three trials ranged in size from 54 to 547 patients and detected no significant difference in skin toxicity when trolamine was compared to Solaris lotion [63], Aquaphor [60], RadiaCare [60], Placebo [60] or standard care [59]. There is no consistent evidence supporting the use of trolamine for the prophylaxis of acute radiation-induced skin reactions.

A variety of other prophylactic topical agents have been tested since 2004 [7, 64-68]. No significant difference in acute skin toxicity was detected between Theta-Cream and Bepanthol lotion [64]. Similarly, wheat grass extract was not found to reduce skin toxicity when compared to a simple barrier cream (Sorbolene) [68]. Both of these trials had a very small sample of patients with breast cancer ($n=20$). Enomoto et al. [66] conducted a small ($n=30$), double-blinded RCT and found the mean RTOG grade to be 24% lower in a group using topical RayGel (an aqueous based formulation containing glutathione and anthrocyanins) compared with a placebo; however, this did not reach significance (p not reported).

Three other trials did reach statistical significance. Graham et al. [7] conducted an open-label, intra-individual comparison ($n=61$) of Cavilon No-Sting barrier film and Sorbolene on the post-mastectomy chest wall. The barrier film was randomised between the right or left aspect of the chest wall. The barrier film statistically significantly reduced the area under the curve of the RTOG grades ($p=0.005$). In addition, the rate of moist desquamation was less in the barrier film group (33% vs. 46%; $p=0.096$), and Likert scales showed a significant reduction in pruritus ($p=0.019$). A small ($n=15$) cohort study [65] detected a reduction in mean RTOG grade ($p<0.05$) in favour of silver leaf nylon dressings for patients whose perineum was included in the treatment field(s). This study was limited by the use of historical controls and it is unclear exactly what skin care the control patients received. Finally, Merchant et al. [67] found that an anionic polar phospholipid-based cream significantly reduced skin toxicity grade ($p=0.004$) and a range of patient-reported comfort factors when compared with Aloe vera gel in an intra-individual comparison of paediatric patients ($n=45$). This finding is consistent with a systematic literature review [69], which found no evidence to suggest that topical Aloe vera is effective in preventing or minimising acute radiation-induced skin reactions. Despite this, Aloe vera gel remains one of the most commonly recommended topical skin care agents for patients receiving radiation treatment [6].

1.5.4. Management of Acute Radiation-Induced Skin Reactions

A small number of trials have investigated the efficacy of topical agents for the management of acute radiation-induced skin reactions. Studies have been classified as management trials if the test agent commenced after the development of an acute skin reaction, and the trial aimed to reduce the impact of that reaction. The CCOSCGG review [41] identified five management trials. These trials examined a range of products (corticosteroid creams, sucralfate cream, hydrocolloid dressings and a moisture vapour permeable dressing) and no agent was found to significantly reduce the impact of acute radiation-induced skin reactions. The following section intends to provide an overview of the literature regarding the management of skin reactions (particularly moist desquamation) published since the CCOSCGG review [41]. It is not intended as a comprehensive systematic review, and only full text, English language articles available from the University of Otago have been included in this literature update. A total of nine studies were identified and are summarised in Appendix C.

A number of trials investigated agents that create or maintain a moist wound healing environment [70-73]. A moist wound environment has been shown to provide an optimal environment for epithelisation and tissue growth in non-radiation induced wounds. An overview [74] of the principles of moist wound healing state that the technique prevents tissue dehydration, accelerates angiogenesis, increases the breakdown of dead tissue, stimulates growth factors and decreases pain.

Two studies [70, 71] investigated the use of topical honey for the management of acute skin reactions in patients receiving radiation therapy for breast cancer. Honey is well known for its antibacterial, anti-inflammatory and analgesic properties [75]. It has been investigated for the management of superficial burns and open wounds as it provides a moist wound healing environment and promotes granulation and epithelisation. The wound healing environment is further optimised as honey has a high nutrient content, high acidity and a high osmolarity [71, 75]. A single-blinded, RCT by Molenaar et al. [70] compared honey gauze to paraffin gauze in patients with RTOG grade 3 skin toxicity (moist desquamation). This trial closed early due to low accrual (n=21), although it did demonstrate a non-significant trend towards faster healing time, increased patient satisfaction and increased patient comfort in the honey arm. Wound healing was assessed from photographs by a blinded physician and visual analogue scales were used to assess the patients' experience of their skin reaction. This trial was reported as a letter to the editor, and as such limited information was available regarding the methodology.

A larger (n=150) RCT [71] concluded that the combination of topical honey and oral pentoxifylline (PTX) significantly ($p<0.0001$) reduced the area of radiation burn compared with sulfadiazine cream alone. This trial also reported that combination sulfadiazine and PTX is superior to sulfadiazine alone. The methodology and results of this trial are difficult to understand and it is unclear when the interventions commenced or whether the trial was blinded. During wound assessments the researchers measured the area of the “radiation burn”; however this term is ambiguous and could refer to any reaction from mild erythema to necrosis.

Like honey, hydrogel creates a moist wound healing environment. Two studies [72, 73] investigated hydrogels for the management of moist desquamation. Hydrogel conforms to the skin surface and has been reported as providing a cooling effect on the skin [72]. A hydrogel dressing is the current standard of care for moist desquamation at the WBCC. MacMillan et al. [72] conducted a large (n=357), statistically powered, open-label RCT to compare a hydrogel with a dry dressing over a range of treatment sites. This group found that moist desquamation healed more slowly with a hydrogel dressing ($p=0.03$) and provided no significant difference to patient comfort. This trial was the second phase of the study by Wells et al. [44] investigating the effect of sucralfate cream on the prophylaxis of acute-radiation induced skin reactions. Application of the dressings commenced at moist desquamation and patients were randomised prior to developing moist desquamation. Blinding was not possible due to the obvious differences between a gel dressing and a dry dressing.

In contrast to the above findings, Gollins et al. [73] found that the likelihood of moist desquamation healing (based on tracings of the wound) was greater with a hydrogel when compared to gentian violet (GV) (HR 7.95; 95%CI 2.20-26.68) in patients receiving treatment to the breast, chest wall or head and neck. This trial was statistically powered and aimed to recruit 80 patients. Instead it was terminated after only 33 patients due to a clear advantage in favour of the hydrogel. In addition, Gollins et al. [73] reported a number of potential disadvantages associated with GV. The antiseptic solution reportedly forms a dry crust over the wound, which impairs cell migration. It has also been found to be carcinogenic in animal models. For these reasons GV is a poor choice as a skin care agent and has the potential to do more harm than good. Further studies investigating hydrogels for the management of moist desquamation are needed.

A variety of other dressings have been investigated for managing acute skin toxicity. Mak et al. [76] conducted a single-blinded RCT (n=146) to compare a non-adherent absorbent dressing to GV in the management of moist desquamation in patients receiving radiation to the head and neck. No

significant differences in healing time, mood disturbance, appearance, social interaction or neck mobility were found. A very small (n=12), single-blinded, intra-individual comparison by Vavassis et al. [77] detected no significant improvement in RTOG grade when comparing silver-leaf dressings and silver sulfadiazine cream. Although statistical significance was not reached, pain control was subjectively superior in 67% of patients in the silver-leaf dressing arm and 50% of patients asked for the silver-leaf dressing to be used bilaterally due to improved pain control.

One study investigated HA cream for the management of radiation-induced skin reactions. Kirova et al. [78] conducted a large (n=200), open-label RCT comparing HA cream to a placebo emollient cream in patients receiving radiation treatment to the breast or chest wall. Application of the creams commenced when the patient developed a RTOG grade 1 reaction. The primary endpoint was “failure” (interruption of treatment due to erythema) or “success” (disappearance of erythema after 30 days). Other measures included RTOG grade, colorimetric assessment, pain (visual analogue scale) and quality of life (European Organisation for Research and Treatment of Cancer). No significant difference was detected in any of these measures. Unlike most of the other management trials, healing of moist desquamation was not included as a specific measure in this study. It appears that the use of the study creams continued when moist desquamation was present. The application of emollient creams on moist desquamation is strongly discouraged at the WBCC due to the risk of introducing an infection.

Two studies [8, 21] investigating Mepilex Lite for the management of acute radiation-induced skin toxicity have reported promising results. These trials will be discussed further in the next section.

1.6. Mepilex Lite

Mepilex Lite (Mölnlycke Health Care AB, Göteborg, Sweden) is a thin, self-adhering, absorbent, soft silicone dressing designed for the management of non to low exudating wounds and burns (Figure 1.4). It can also be used as a physical protection layer for compromised or fragile skin [79]. The dressing consists of:

1. A soft silicone wound contact layer called Safetac
2. A thin, flexible pad of polyurethane foam to absorb exudate
3. An outer film which is vapour permeable and water proof (though not shower proof)

The Safetac wound contact layer is designed to minimise epidermal stripping and trauma on removal. Safetac gently adheres to dry skin and seals around wound margins to create an undisturbed moist wound healing environment. The thin foam pad is highly conformal and can be cut to suit various wound shapes and locations. It can be left in place for up to seven days, depending on the state of the wound and dressing [79].

A case study conducted in Scotland and Sweden by MacBride et al. [21] evaluated patient comfort and experience when using Mepilex Lite dressings for the management of brisk erythema and moist desquamation of the breast or head and neck. This small (n=16) study reported that most patients found the dressing comfortable to wear and in many cases it had a positive impact on their skin reaction and daily activities (e.g. sleeping, wearing clothes and wearing a seatbelt). Mepilex Lite resulted in a consistent improvement in all aspects of the patients' skin reactions. It should be noted that two patients stopped using the dressing due to severe itching and that the dressings did not always remain in place in awkward areas.

Following this, Diggelmann et al. [8] conducted a small (n=24), intra-individual controlled trial comparing Mepilex Lite dressings to aqueous cream for the management of erythema in patients undergoing radiation therapy to the breast. The extent of erythema and the patients' subjective symptoms were measured using the Modified Radiation Induced Skin Reaction Assessment Scale (RISRAS). The dressings were found to significantly ($p<0.001$) reduce the extent of radiation-induced erythema and improved patient comfort. None of the patients in this trial experienced an adverse reaction to Mepilex Lite. This study also sought to quantify the effect of Mepilex Lite dressings on dose build up and surface skin temperature. The dressing was found to have no effect on skin

temperature and created a negligible (0.5mm) bolus effect, indicating that it is safe to wear during radiation treatment. This study aimed to determine the effect of the dressings on erythema and not moist desquamation, which clinically is a more relevant and significant endpoint. This research has led to the current study which aims to evaluate the effect of the dressings on the management of the full range of acute radiation-induced skin reactions.

Diggelmann et al. [8] hypothesised that Mepilex Lite reduced radiation-induced skin reactions by providing physical protection against damage caused by abrasion and friction. Further damage to irradiated skin, through friction from clothing or other tissues, could interfere with the proliferation of stem cells in the basal layer and slow the healing process. This concept is supported by other researchers [3, 7]. Porock and Kristjanson [3] promote the reduction of friction or irritation in order to maintain the integrity of the superficial epidermis layer for as long as possible. An intact stratum corneum allows the basal stem cells more time to reproduce and therefore reduces the likelihood of moist desquamation occurring [7].

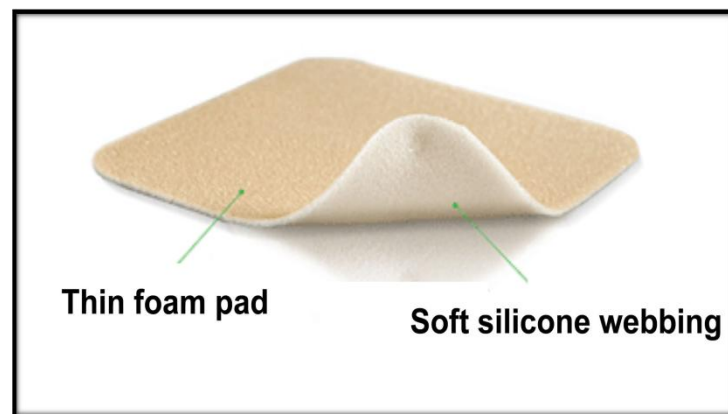


Figure 1.4 Mepilex Lite Dressing

1.7. Aim and Objectives

Aim

The overarching aim of the current trial was to investigate whether Mepilex Lite dressings are superior to standard care in reducing the extent of radiation-induced skin reactions in patients receiving treatment for breast cancer post-mastectomy.

Primary Objective

- To determine whether Mepilex Lite dressings are superior to standard care in reducing the overall severity of acute radiation-induced skin reactions.

Secondary Objectives

- To determine whether Mepilex Lite dressings reduce the incidence of moist desquamation.
- To determine whether Mepilex Lite dressings increase the time to onset of moist desquamation compared with standard aqueous cream.
- To determine whether Mepilex Lite dressings decrease the time to healing compared to the standard dressing used in the different departments.

Primary Endpoint

- Modified RISRAS scores.

Secondary Endpoints

- Incidence of moist desquamation.
- Time to onset of moist desquamation.
- Time to healing.

2. METHODOLOGY

This trial is a multicentre, open-label, randomised, intra-individual comparison of Mepilex Lite dressings versus standard care during post-mastectomy irradiation in New Zealand. The four radiation therapy centres involved are located in Wellington, Palmerston North, Dunedin and Auckland. This honours thesis reports the results of the first 10 patients available for analysis at the WBCC. Recruitment for this trial is continuing at all four centres at the time of writing.

The trial was approved by the Multi-region Ethics Committee in April 2010 and in May 2011 (MEC/10/04/033); and is registered with the Australia New Zealand Clinical Trials Registry (ACTRN12611000718943).

2.1. Participants

Eligibility

Inclusion Criteria: all women aged over 18 years who received post-mastectomy radiation therapy for breast cancer and had not had a reconstruction. The post-mastectomy chest wall provides a uniform surface that receives a relatively homogenous dose, compared with other sites where skin reactions are common. It is therefore an ideal test bed for the comparison of topical interventions for the prevention and management of acute radiation skin toxicity [7].

Exclusion Criteria: previous radiation therapy to the chest wall, metastatic disease, breast reconstruction, impaired mobility, Karnofsky performance status scores of less than 70. Patients that were unable to return to the department for skin assessments once a week after treatment for up to six weeks were also excluded.

Description of Radiation Therapy Treatment

Radiation was given as 50Gy in 25 fractions or a biologically equivalent dose at the Radiation Oncologist's discretion. Several regimens are in common use, but intra-individual comparison negates this variable. Information on planning technique, dose, bolus procedure, chemotherapy and hormone therapy was recorded

Patients were treated in the supine position on an elevated board. Radiation therapy to the chest wall was usually delivered using 6MV or a combination of 6MV and 18MV photon beams applied tangentially. Bolus of 3mm was applied to the chest wall daily. If required, the supraclavicular and axilla lymph nodes were treated with an antero-lateral oblique photon field(s) with or without a semi opposed posterior axilla field.

Participant Numbers

This trial aims to recruit 80 patients over one year, although this thesis only reports on the findings of the first 10 patients available for analysis at the WBCC. The exact incidence of moist desquamation in this population is unknown. The incidence will be determined from this trial so that any power calculations for a larger multinational trial concerning the impact of Mepilex Lite on moist desquamation can be made. A previous intra-individual RCT [7] investigating two skin care regimes on the post mastectomy chest wall recruited 61 patients and reached statistical significance.

Consent

Patients commenced radiation treatment after receiving information about the trial verbally from their radiation oncologist in the form of a participant information sheet (Appendix D) at their planning CT scan. Patients were given further opportunity to discuss the trial with the research assistant and gave written informed consent on day one or two of radiation treatment (Appendix E).

Participants act as their own controls

This was an intra-individual comparison where patients acted as their own controls (Figure 2.1). At the first sign of erythema, the erythematous area was divided into two equal halves; one half was covered in Mepilex Lite (intervention), the other treated with aqueous cream (control). An alert was attached to the patient's treatment sheet to prompt the treatment staff to check for erythema daily and inform the radiation therapy research assistant at the first sign of erythema. The area treated with Mepilex Lite was randomly assigned. Using intra-individual controls was expected to circumvent confounding patient-related and treatment-related factors. Randomisation was expected to circumvent the effect of small dose differences between the dressed and undressed patches.

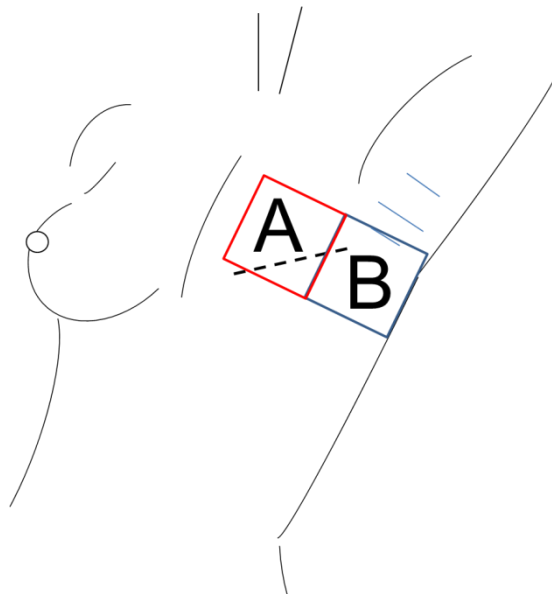


Figure 2.1 Intra-individual comparison.

The first area of erythema was divided into two patches: "A" and "B". Mepilex Lite was randomised to one of the patches with the other patch acting as a control patch.

Randomisation

The first erythematous skin area on the chest wall was divided into either inferior and superior halves or medial and lateral halves by the radiation therapy research assistant. Mepilex Lite dressings were

allocated randomly by pre-prepared computer generated randomisation charts, which were created by a Biostatistician at the University of Otago, Wellington. The dressings were allocated to either superior/left or inferior/right depending on how the erythematous patch was orientated and had been divided. Randomisation was conducted via a randomisation form (Appendix F) which was sent by fax to the principal investigator (Dr Patries Herst) at the University of Otago, Wellington. The principal investigator had no direct involvement with the patients.

Blinding

Neither the patients nor the research assistant were blinded. It was impossible to blind the patient as the two skin treatment regimens are very different in appearance. The research assistant who divided the area of erythema also scored the visible extent of the skin reaction.

Initial Skin Assessment

An Initial Skin Assessment Form (Appendix G) was completed for each patient during their first week of radiation treatment. This assessment was designed to record details of the patients' radiation construct as well as other personal and treatment related factors that may have influenced their likelihood of developing a severe radiation-induced skin reaction (see Chapter One, section 1.3). The Initial Assessment was carried out by either the research assistant, the Clinical Nurse Specialist (Radiation Oncology) or the review clinic radiation therapist.

Adverse Events and Discontinuation

The dressings are made of a very thin foam with silicone webbing. They do not contain any chemicals and therefore do not react with the skin; however itching has been reported by one case study [21]. If discontinuation of Mepilex Lite or aqueous cream occurred due to allergy (or another patient reason), substitution of alternative creams was at the treating clinician's discretion. Application of the agent causing the allergy would cease and the patient would withdraw from the study.

2.2. Procedure

All patients were encouraged to apply aqueous cream over the entire chest wall twice daily until the first sign of erythema. After erythema developed, patients were instructed to continue applying aqueous cream to the remainder of the chest wall that was not included in the study area. All patients were advised on the general skin care guidelines [43] outlined in Chapter One, section 1.5.2, excluding the use of Calendula cream. Hydrocortisone 1% was prescribed as required for pruritus as it was considered an essential component of standard care.

2.2.1. Intervention Patch

1. A Mepilex Lite dressing was cut to size and applied to the skin patch randomised to the intervention arm. Dressings were replaced when necessary (approximately every 3 or 4 days). Only the first erythematous area was considered for randomisation whilst any other erythematous skin was treated with aqueous cream.
2. The exact position of the dressing was indicated with a semi-permanent marker pen so that when the dressing was removed during treatment or before showering, it could be reapplied in exactly the same position. When dressings were removed they were placed on a clean surface (e.g. paper towel) with the adhesive side facing up. Dressings were only reused if they were clean.
3. Diggelmann et al. [8] had shown that radiation therapy can be given through Mepilex Lite with a very small bolus effect. For this trial the dressings were removed during treatment because they may have obscured treatment positioning tattoos in some patients.
4. Mepilex Lite continued for the duration of radiation therapy and continued after completion of treatment until the skin reaction resolved.
5. If moist desquamation developed in the Mepilex Lite area, this continued to be treated with Mepilex Lite. In this situation, dressings were replaced daily until the skin healed.

2.2.2. Control Patch

1. Aqueous cream was applied by the patient twice a day to treat the control patch.
2. If moist desquamation developed in the control patch, it was covered with the standard dressings used in the different centres. At the WBCC, areas of moist desquamation were dressed with a hydrogel (Solosite), covered with a non-adherent wound contact layer (Cuticerin) and an absorbent pad (Combine).

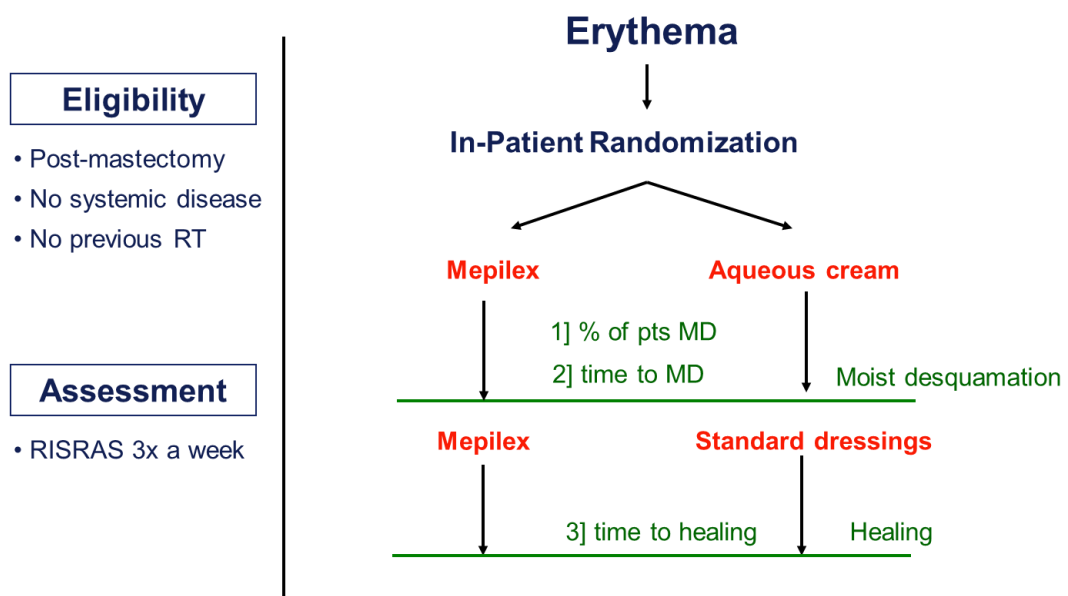


Figure 2.2 Schematic diagram of study regime

2.3. Measurements

Modified Radiation-Induced Skin Reaction Assessment Scale (RISRAS)

The Modified RISRAS [21] was used to assess the extent of the acute radiation-induced skin reaction in both the intervention and control patches (Table 2.1). These assessments occurred three times a week from the onset of erythema (Monday, Wednesday and Friday) and continued once a week after the completion of radiation treatment for up to six weeks or until the skin reaction had resolved. The radiation therapy research assistant was responsible for filling out the researcher component of the RISRAS assessments, which assessed the outward signs of the skin reaction. When the research assistant was unavailable, skin assessments were carried out by either the Clinical Nurse Specialist (Radiation Therapy) or the Review Clinic Radiation Therapist. All three assessors attended a pre-trial workshop to ensure RISRAS scoring was consistent and to minimise inter-scorer variability. Patients were asked by the research assistant to score each of the patient components of the RISRAS for both the intervention and control patch.

The RISRAS was developed and validated by Noble-Adams [9, 14, 20] and later modified by MacBride et al. [21]. This scale has a number of advantages [4, 69] over the more commonly used RTOG [48] or NCI-CTC [49] acute skin toxicity scales (Appendix B). Firstly, the RTOG and NCI-CTC scales pool together different types of reactions. For example, faint erythema and dry desquamation are given the same score as are bright erythema and patchy moist desquamation. The RISRAS applies a separate grade for erythema, dry desquamation and moist desquamation and is able to detect small differences in skin reaction severity. Secondly, the RISRAS provides more detailed information on the area of skin affected by the reaction. Finally, the RISRAS incorporates both a professional-rated (researcher component) score based on the outward signs of a skin reaction (erythema, dry and moist desquamation and necrosis) and a patient-rated (patient component) personal experience of the skin reaction (discomfort, itchiness, burning, effect on daily life); whereas RTOG and NCI-CTC provide no indication on the subjective symptoms of skin reactions.

Moist Desquamation

The presence of moist desquamation in the study area, the date it occurred and its location (i.e. intervention and/or control patch) was recorded for each patient. Moist desquamation was also recorded as part of the RISRAS assessment. At the completion of radiation treatment, patients were educated on how to recognise moist desquamation and were advised to contact the research assistant and return for assessment if it developed between scheduled assessments.

Time to healing was defined as the time it took for complete re-epithelisation. In the case of moist desquamation this meant that there was new pink skin covering the entire wound area.

Exit Questionnaire

At the completion of the trial, patients were given an exit questionnaire (Appendix H) which allowed them the opportunity to comment on different aspects of participating in the trial.

Dose

Dose comparisons were made between the intervention and control patches. Thermo luminescent dosimeters (TLDs) were used on all patients enrolled at the Dunedin Oncology Department to determine and compare the actual dose delivered to the intervention and control patches. TLDs were not used for this cohort of patients due to resource constraints in the Medical Physics Department at the WBCC.

At the WBCC, estimates of skin dose were made using the point dose function on the treatment planning system (Eclipse Version 8.9, Varian Medical Systems Inc, Palo Alto, CA). The point dose was assessed at five locations in each of the study patches and the average skin dose was calculated for each patch (Figure 2.3). The aim was to gain an estimate of the relative skin dose in each patch, due to the difficulties in determining actual dose in the build-up region. A tracing of the study area and translational measurements from the AP tattoo to each point of interest were taken. These measurements were used to locate each point of interest on the treatment planning system where the dose assessments were made.

Table 2.1 Modified Radiation-Induced Skin Reaction Assessment Scale (RISRAS)

RISRAS (total scores between 0 and 36)^a					
Researcher Component (total scores between 0 and 24)					
Erythema (E)	0 Normal skin	1 Dusky pink	2 Dull red	3 Brilliant red	4 Deep red-purple
Dry Desquamation (DD)	0 Normal skin	1 ($<25\%$) ^b	2 (25%-50%)	3 (50%-75%)	4 ($>75\%$)
Moist Desquamation (MD)	0 Normal skin	1.5 ($<25\%$)	3.0 (25%-50%)	4.5 (50%-75%)	6 ($>75\%$)
Necrosis (N)	0 Normal skin	2.5 ($<25\%$)	5.0 (25%-50%)	7.5 (50%-75%)	10 ($>75\%$)
Patient Component (total scores between 0 and 12)					
Symptoms	Not at all		A little	Quite a bit	Very much
<i>Do you have any tenderness, discomfort of pain of your skin in the treatment area?</i>	0		1	2	3
<i>Does your skin in the treatment area itch?</i>	0		1	2	3
<i>Do you have a burning sensation of your skin in the treatment area?</i>	0		1	2	3
<i>To what extent has your skin reactions and your symptoms affected your day to day activities?</i>	0		1	2	3

^a Individual scores for each item are added up to give a total score for the researcher and patient components of the scale. Adding the researcher and patient component scores together gives the total combined RISRAS score.

^b Percentage of surface area of affected skin.

Adapted from MacBride et al. [21]

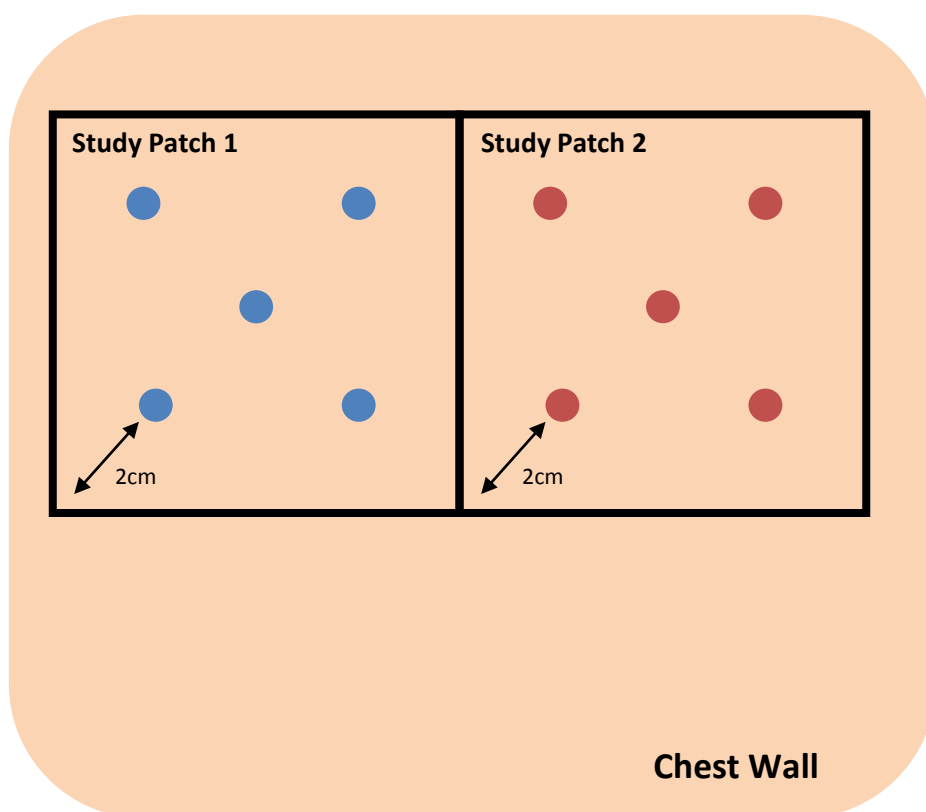


Figure 2.3 Location of point dose estimates.

The location of point dose estimates are represented by the blue (Patch 1) and red (Patch 2) dots. One measurement was taken at the centre of each patch. The other measurements were taken at a point 2cm from each patch corner on a diagonal line towards the centre.

2.4. Trial Timeline at the Wellington Blood and Cancer Centre

The Mepilex Lite trial timeline is displayed in Figure 2.4. Post-mastectomy patients requiring radiation therapy were identified by the research assistant from the WBCC radiation therapy booking system (ARIA Time Planner, Varian Medical Systems, Palo Alto, CA). Eligibility was assessed through examination of the patient's clinical notes. If eligible, a participant information sheet (Appendix D) was placed with the patient's treatment folder and their Radiation Oncologist was informed.

Eligible patients first received verbal and written information about the trial at their planning CT scan. The participant information sheet was given to the patient by their Radiation Oncologist or registrar and they were shown an example of a Mepilex Lite dressing. Most patients also gave informed consent to radiation therapy at this stage. The patients had several weeks between their CT scan and the start of radiation treatment to read about the trial and consider their participation.

On the day of the first or second fraction of radiation treatment eligible patients met with the research assistant. The research assistant re-explained the trial and answered any further questions from the candidate and/or their support person(s). Consent was gained by the research assistant if the patient was willing to participate. All candidates were provided with verbal and written general skin care advice at this stage and were instructed to commence application of aqueous cream to the chest wall. A randomisation form (Appendix F) was filled in by the research assistant and faxed to the Principal Investigator. During the first week of radiation treatment the initial skin assessment was completed.

At the first sign of erythema, treatment staff informed the research assistant. The erythematous area was divided and the intervention commenced. The patients were given a supply of Mepilex Lite and were instructed on how to use the dressing. A tracing of the study area was also taken so that the markings on the skin could be replaced as necessary and to assist with the dose estimates. At this stage, three weekly RISRAS assessments commenced for the duration of the patient's radiation treatment. At the completion of treatment, patients were assessed once a week for up to six weeks and were instructed to contact the research assistant if moist desquamation developed between assessments. At six weeks post-treatment or when the skin reaction resolved, patients were asked to complete the exit questionnaire and the dose assessment was performed.

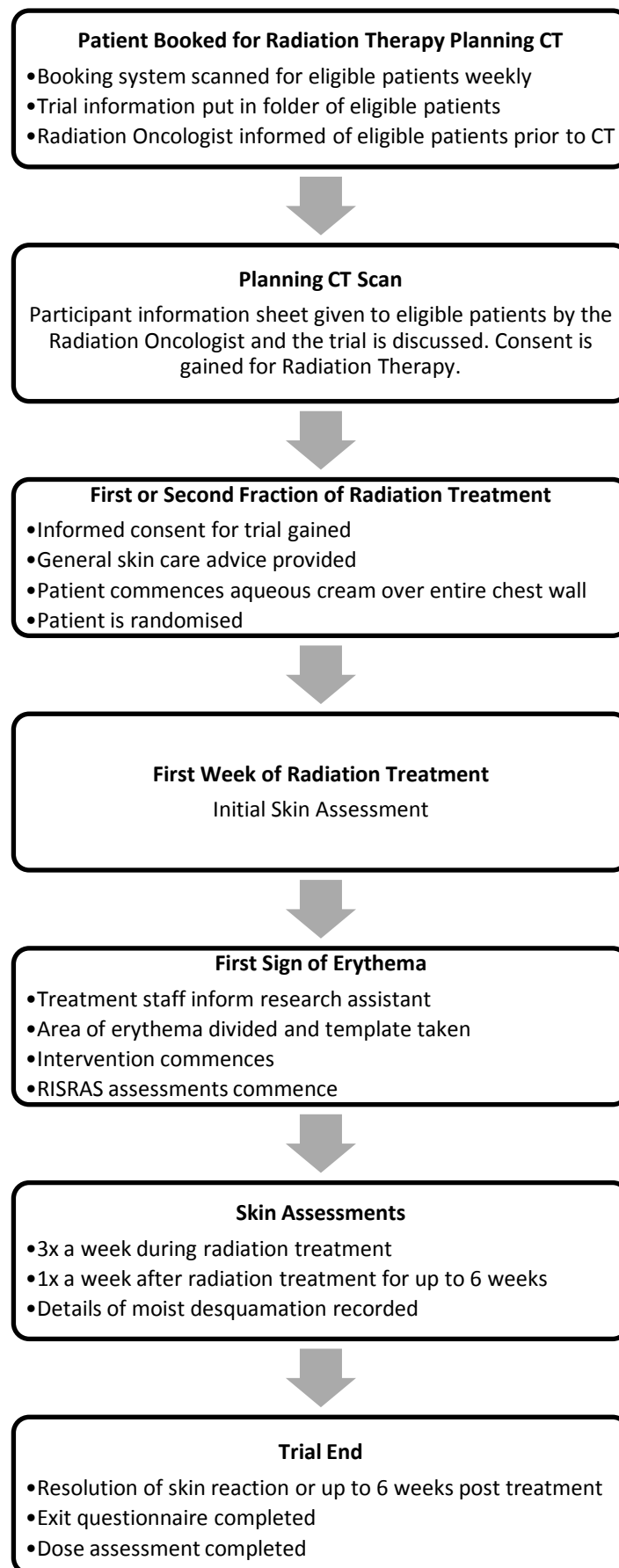


Figure 2.4 Trial timeline

2.5. *Data Collection and Statistical Analysis*

The radiation therapy research assistant used the patient appointment system ARIA Time Planner (Varian Medical Systems, Palo Alto, CA) to identify potential candidates. All measurement data was entered into Windows Excel 2007 (Microsoft Corporation, Redmond, WA) spread sheets by the research assistant. This data was emailed to the central trial centre prior to analysis. Dose estimates were made from the treatment planning system Eclipse (Varian Medical Systems, Palo Alto, CA).

Paired sample, two-tailed student t-tests (SPSS v19, Armonk, NY) were used to determine the statistical significance of differences between the Modified RISRAS scores of Mepilex Lite and control skin patches, with $p < 0.05$ considered statistically significant.

2.6. Funding

The salary of the Principal Investigator (Dr Ptries Herst) was paid by the University of Otago. The salaries of the Clinical Nurse Specialist (Ruth Wickens) and the Review Clinic Radiation Therapist (Jenni Reeves) were paid by the Capital and Coast District Health Board. The salary of the radiation therapist research assistant (Dean Paterson) was paid by a University of Otago Research Grant. The fee for the Bachelor of Radiation Therapy (Honours) programme was funded by grants from the Rouse Education Trust, the Cancer Society (Wellington Division), the WBCC Continued Professional Development fund and the New Zealand Breast Cancer Foundation.

Mepilex Lite dressings were supplied free of charge by Mölnlycke Health Care AB (Göteborg, Sweden). All other costs, including patient travel reimbursement for follow-up assessments, were funded by a University of Otago Research Grant. There were no known conflicts of interest between research staff at the WBCC or University of Otago and Mölnlycke Health Care AB.

2.7. Amendments

It was observed that skin tended to appear dryer under the Mepilex Lite dressings when compared to the control patches. Therefore two amendments were made to the original trial design:

1. The first amendment allowed patients to use aqueous cream as a soap substitute over both the control and intervention patches due to its emollient properties.
2. The second amendment stipulated that patients who did not develop moist desquamation in the study area and scored '0' on the patient component of the RISRAS could stop applying the Mepilex Lite dressing from the three week follow-up onwards. These patients would continue to use aqueous cream over both the control and intervention patches until their skin reaction (erythema) fully resolved.

3. RESULTS

3.1. *Patient Recruitment and Flow*

Recruitment for this analysis occurred between March and June 2011. Details of the accrual process are summarised by the CONSORT diagram in Figure 3.1. During this period 24 women had a planning CT for post-mastectomy irradiation at the WBCC. Of these patients, eight were ineligible as they were either: unavailable for follow-up (n=3), had systemic disease (n=2), had a breast reconstruction (n=1), had previous mantle field irradiation (n=1) or had an open wound on the chest wall (n=1). The three patients unavailable for follow-up were from the South Island of New Zealand. The remaining 16 eligible patients were provided verbal and written information regarding the trial at their planning CT appointment. One of these patients declined radiation therapy at their planning appointment and was therefore unable to participate.

Informed consent was obtained at the first or second fraction of radiation treatment. Three patients declined participation due to the time commitment involved. A total of 12 patients gave consent and were randomised. Two of these patients are excluded from the RISRAS and moist desquamation analysis. One patient withdrew after wearing a Mepilex Lite dressing for one day, citing that the dressing kept falling off. This patient (WGN07) completed an exit questionnaire and was therefore included in the exit questionnaire analysis only. The other patient did not understand where to place the Mepilex Lite dressings and was excluded from all analysis due to non-compliance. Ten patients completed the trial and are included in this analysis.

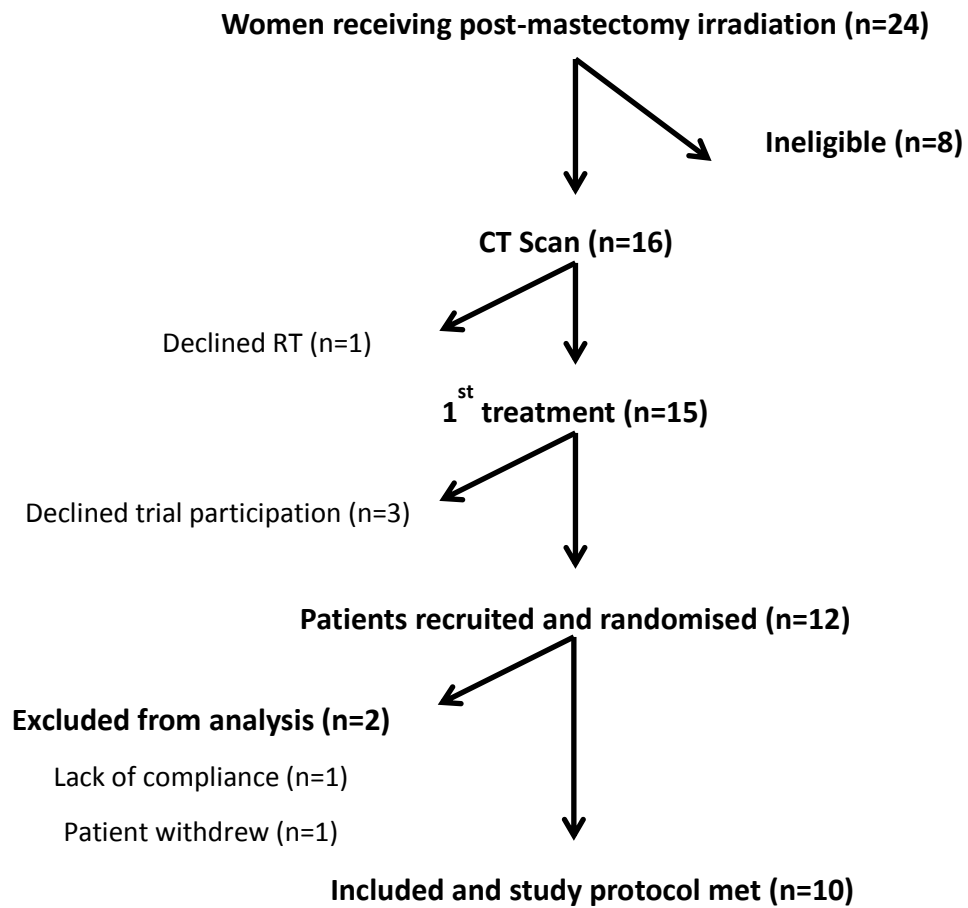


Figure 3.1 CONSORT Diagram of participant flow

3.2. Patient Demographics

Demographics of the 10 patients available for analysis were collated from the initial skin assessment and are presented in Table 3.1. The use of intra-individual controls circumvents the confounding effect of the patient-related and treatment-related factors that were discussed in section 1.3. A correlation analysis is planned for the final analysis of the results of all 80 patients on the larger trial to determine the effect of these variables on the likelihood of developing a severe reaction.

3.2.1. Personal Construct

Age: Patient age ranged from 33 to 66. The median age of the patients was 50.5 years. Approximately 70-75% of all breast cancers are diagnosed in women 50 years of age and over [1], which suggests that patients in this cohort are younger than the national average.

Weight and Separation: Weight ranged from 48.4Kg to 107.6Kg. The mean weight was 75.2Kg (SD 20Kg). Breast separation was measured as a straight line between the medial and lateral treatment field borders. There was a statistically significant correlation between weight and separation ($R^2=0.824$, $p<0.001$).

Ethnicity: Eight (80%) patients identified themselves as New Zealand European or Pakeha. One (10%) patient was Maori and one (10%) was Indian.

Skin Phenotype: The Fitzpatrick Skin Type [80] was used to describe skin phenotype. The most common skin type was type III (40%), followed by type II (20%) and type IV (20%). One patient (10%) was type I and one (10%) was type V. The Fitzpatrick Skin Type is available in Appendix G.

Diagnosis: Seven (70%) patients were diagnosed with infiltrating ductal carcinoma (IDC). One of these patients had a micropapillary IDC and another had inflammatory IDC. Two (20%) patients were diagnosed with invasive lobular carcinoma (ILC) and one (10%) had a malignant phyllodes tumour. The majority of patients (60%) had a grade 3 tumour and 30% had a grade 2 tumour. Phyllodes tumours are not given a grade. Six (60%) of the patients were estrogen and progesterone receptor positive and two (20%) were human epidermal growth factor receptor 2 (Her2) positive. The Her2 positive patients received concurrent Herceptin.

Lifestyle: Only one (10%) patient described themselves as a current smoker and reported smoking between two and five cigarettes a day. Four (40%) patients were ex-smokers and quit smoking between four and 14 years earlier. Their nutritional status was described as “good” by seven (70%) patients and “excellent” by the remaining three (30%) patients.

Co-morbidity: An allergy to some types of medical tape, adhesive or plaster was described by 4 (40%) of the patients. None of these patients had a reaction to the Mepilex Lite dressings. Three (30%) patients had a history of hypertension. One (10%) patient had previously had contralateral breast cancer and received both radiation and chemotherapy for this in 2007. Another patient (10%) had Milroy disease, and was therefore unable to have an axillary dissection or chemotherapy.

3.2.2. Therapy Construct

Surgery: All patients (100%) had a mastectomy. Eight (80%) patients also had an axillary lymph node dissection (ALND). Of the two patients that did not have an ALND, one (10%) had Milroy disease and the other (10%) had a malignant phyllodes tumour.

Radiation Therapy: The majority of patients received the WBCC standard dose for post-mastectomy irradiation of 50Gy in 25 fractions over five weeks delivered using a tangential beam arrangement. Only one (10%) patient deviated from this protocol. This patient received 45Gy in 25 fractions using a tangential beam arrangement with an additional lowly weighted photon beam perpendicular to the tangents. This beam arrangement was chosen as it improved dose homogeneity and reduced dose “hot spots” in this patient. Six (60%) patients had radiation delivered to the chest wall with 6MV photons only and four (40%) had a combination of 6 and 18MV photons. All patients (100%) had 3mm of bolus applied to the entire chest wall daily. Eight (80%) patients received irradiation to their supraclavicular nodes and four (40%) also received irradiation to their axillary nodes. Only one (10%) patient received a boost. This was given as 10Gy in five fractions using 6MeV electrons and was outside the study patches.

Chemotherapy: Chemotherapy was given prior to radiation therapy in seven (70%) patients. Six (60%) patients received four cycles of adriamycin and cyclophosphamide (AC) followed by weekly paclitaxel for three months. One (10%) patient received four cycles of docetaxel and cyclophosphamide. This patient had previously received AC chemotherapy for contralateral breast cancer in 2007 and could not receive further adriamycin due to the risk of cardiomyopathy. One

(10%) patient had inflammatory breast cancer and received chemotherapy prior to her mastectomy. The remainder received chemotherapy post-mastectomy but prior to irradiation.

Herceptin and Hormone Therapy: The two (20%) Her2 positive patients received concurrent Herceptin. Two patients (20%) were also on hormone therapy during radiation treatment; one using tamoxifen and the other with an aromatase inhibitor (AI). Hormone therapy was planned after the completion of radiation treatment for the remaining hormone receptor positive patients.

Table 3.1 Patient Demographics

Patient	WGN01	WGN02	WGN03	WGN05	WGN06	WGN08	WGN09	WGN10	WGN11	WGN12
Age	38	50	49	57	66	33	47	58	51	65
Weight (Kg)	83.6	48.4	72.6	60.9	107.6	73.2	90.3	60.2	101.0	54.1
Separation (mm)	230	173	195	204	269	195	212	202	240	186
Ethnicity	Indian	Pakeha	NZ Maori	Pakeha	Pakeha	Pakeha	Pakeha	Pakeha	Pakeha	Pakeha
Skin Type ^a	V	IV	IV	I	III	II	III	III	II	III
Cancer Construct										
Laterality	Right	Right	Left	Right	Right	Left	Left	Left	Left	Left
Histology	IDC	Phyllodes	IDC	IDC	ILC	IDC	multifocal ILC	IDC	Inflammatory IDC	micropapillary IDC
Grade	3	NA	3	3	2	2	3	3	3	2
Stage	T3N0M0	NA	T1bN2M0	T2N2M0	T3NxM0	T3N1M0	T2N1M0	T2N2M0	T4dN1M0	T3N1M0
Receptor Status:										
ER	-	-	+	-	+	+	+	-	+	+
PR	-	-	+	-	+	+	+	-	+	+
Her2	-	-	-	+	-	-	-	+	-	-
Radiation Construct										
Dose	50Gy/25#	50Gy/25#	50Gy/25#	50Gy/25#	50Gy/25#	50Gy/25#	50Gy/25#	50Gy/25#	45Gy/25#	50Gy/25#
Beams (chest wall)	tangents	tangents	tangents	tangents	tangents	tangents	tangents	tangents	3 field conformal	tangents
Bolus (mm)	3	3	3	3	3	3	3	3	no	3
Boost	no	no	no	yes	no	no	no	no	6/18	no
Energy (chest wall) (MV)	6/18	6	6	6/18	6/18	6	6	6	yes	6
S'clav field(s)	no	no	yes	yes	yes	yes	yes	yes		yes
Chemotherapy	none	none	Neoadjuvant docetaxel & cyclo-phosphamide	Neoadjuvant AC and paclitaxel	none	Neoadjuvant AC and paclitaxel	Neoadjuvant AC and paclitaxel	Neoadjuvant AC and paclitaxel	Pre-surgery AC and paclitaxel	Neoadjuvant AC and paclitaxel
ALND	yes	no	yes	yes	no	yes	yes	yes	yes	yes
Herceptin	no	no	no	yes	no	no	no	yes	no	no
Hormone Therapy	no	no	tamoxifen	no	AI	post-RT	post-RT	no	post-RT	post-RT
Post-surgery Infection	no	no	yes	no	no	no	no	no	yes	no
Smoking history	never	current	ex-smoker	ex-smoker	never	never	ex-smoker	never	never	ex-smoker
Nutrition Status	good	excellent	good	excellent	excellent	good	good	good	good	good
Alcohol (drinks/week)	0	0	10-20	1-3	<1	0	3-10	0	1-3	<1
Co-morbidity										
High blood pressure	no	no	no	no	yes-controlled	no	no	yes	yes-controlled	no
Allergies	no	no	adhesives	plasters/tape	dust mites	no	hayfever	no	some plaster	some plaster
Other	no	no	previous right breast cancer	no	Milroy disease	no	no	no	no	no

+, positive; -, negative; ALND, axillary lymph node dissection; ER, estrogen receptor; Her2, human epidermal growth factor receptor 2; MV, mega-voltage; PR, progesterone receptor

^aFitzpatrick Skin Type [80]

3.3. Dose Distribution

The mean estimated skin surface dose is depicted in Figure 3.2. The mean estimated skin dose was 95.48% (SD 5.60%) of the prescribed dose in the intervention patches and 92.84% (SD 6.10%) of the prescribed dose in the control patches. The small increase in estimated skin dose in the intervention patches was not statistically significant ($p=0.288$). It is therefore unlikely that skin surface dose had a confounding effect on the acute radiation-induced skin reactions observed.

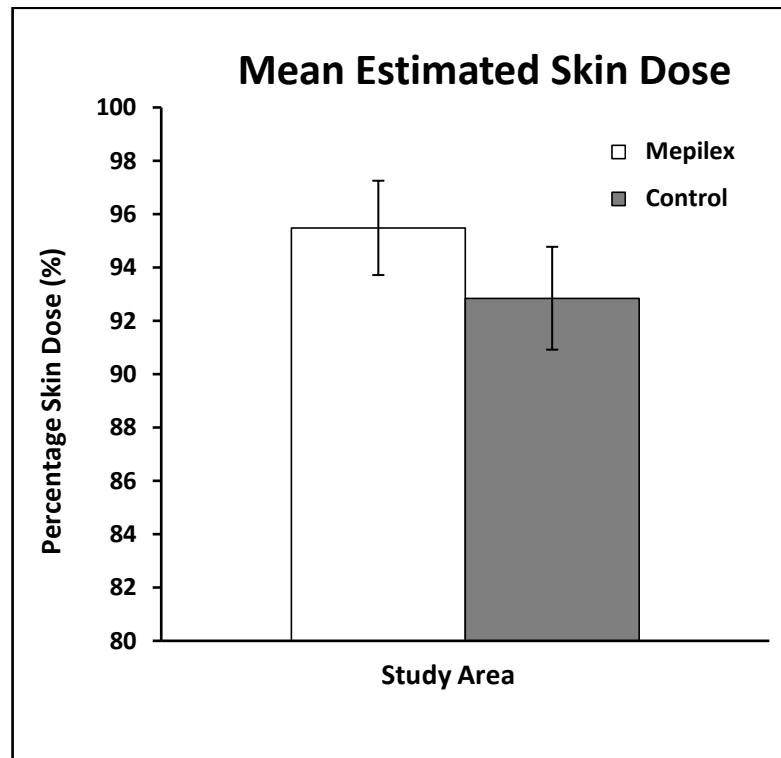


Figure 3.2 Mean estimated skin dose under Mepilex Lite patches (white bar) and control patches (grey bar). Error bars represent the standard error in the mean.

3.4. Onset of Erythema

The erythema dose is the dose at which erythema was first identified by the treating radiation therapists. At this point, the area of erythema was divided into two equal halves and application of the Mepilex Lite dressings commenced. The erythema dose and the time to erythema are displayed in Table 3.2. The erythema dose ranged from 9Gy to 30Gy. The mean dose at erythema was 17.5Gy (SD 6.02Gy) and the mean time to erythema was 11.4 days (SD 4.38 days). The surface area of the study patches ranged from 57.5cm² to 220.5cm² (mean 143.18 cm², SD 54.75cm²).

Table 3.2 Onset of Erythema for Individual Patients

Patient	Erythema Dose (Gy)	Days to Erythema
WGN01	18	15
WGN02	18	12
WGN03	10	6
WGN05	16	9
WGN06	18	11
WGN08	22	14
WGN09	14	8
WGN10	30	20
WGN11	9	6
WGN12	20	13
Mean	17.5	11.4
SD	6.02	4.38
Range	9 to 30	6 to 20

3.5. Modified RISRAS

Figure 3.3 shows the progression of each patient's combined (researcher and patient component) RISRAS scores over the course of the trial. The mean length of time to complete radiation treatment (25 fractions) was 34.4 days. For every patient except one (WGN11), the highest combined RISRAS scores were recorded during either first or second weekly follow-up assessment. In addition, the greatest difference in scores between intervention and control were mostly observed during follow-up assessments. The average RISRAS scores and peak RISRAS scores for the intervention and control patches were compared and are displayed in Table 3.3.

The researcher component of the RISRAS is a measure of the outward signs of the skin reaction, whereas the patient component is a measure of the patient's experience of that reaction. The researcher and patient components are summed to give the combined RISRAS score in each patch. The researcher component consists of a score for erythema, dry desquamation, moist desquamation and necrosis (Table 2.1). Because the previous Mepilex Lite trial (8) compared erythema scores between Mepilex Lite patches and control patches, the erythema scores from the patients in the current trial have been analysed separately to allow for comparison of the results of the two trials.

The statistical significance of the mean differences in the RISRAS scores were compared using the two-tailed paired-samples t-test.

Table 3.3 Comparison of Average and Peak Modified RISRAS Scores

	Mepilex	Control	Mean Difference	95% CI	p-value ^a
Average RISRAS					
Combined Score	2.19	2.98	-0.79	-1.37 to -0.28	0.013 ^b
Researcher Score	1.84	1.90	-0.06	-0.31 to 0.19	0.618
Erythema Score	1.60	1.76	-0.16	-0.28 to -0.04	0.012 ^b
Patient Score	0.35	1.09	-0.74	-1.40 to -0.08	0.031 ^b
Peak RISRAS					
Combined Score	5.85	7.60	-1.75	-4.21 to -0.71	0.142
Researcher Score	4.45	4.15	0.30	-1.11 to 1.71	0.642
Erythema Score	2.90	3.20	-0.30	-0.98 to 0.38	0.343
Patient Score	1.80	4.00	-2.20	-3.95 to -0.45	0.019 ^b

^aPaired Samples t-test (2-tailed)

^bStatistically Significant

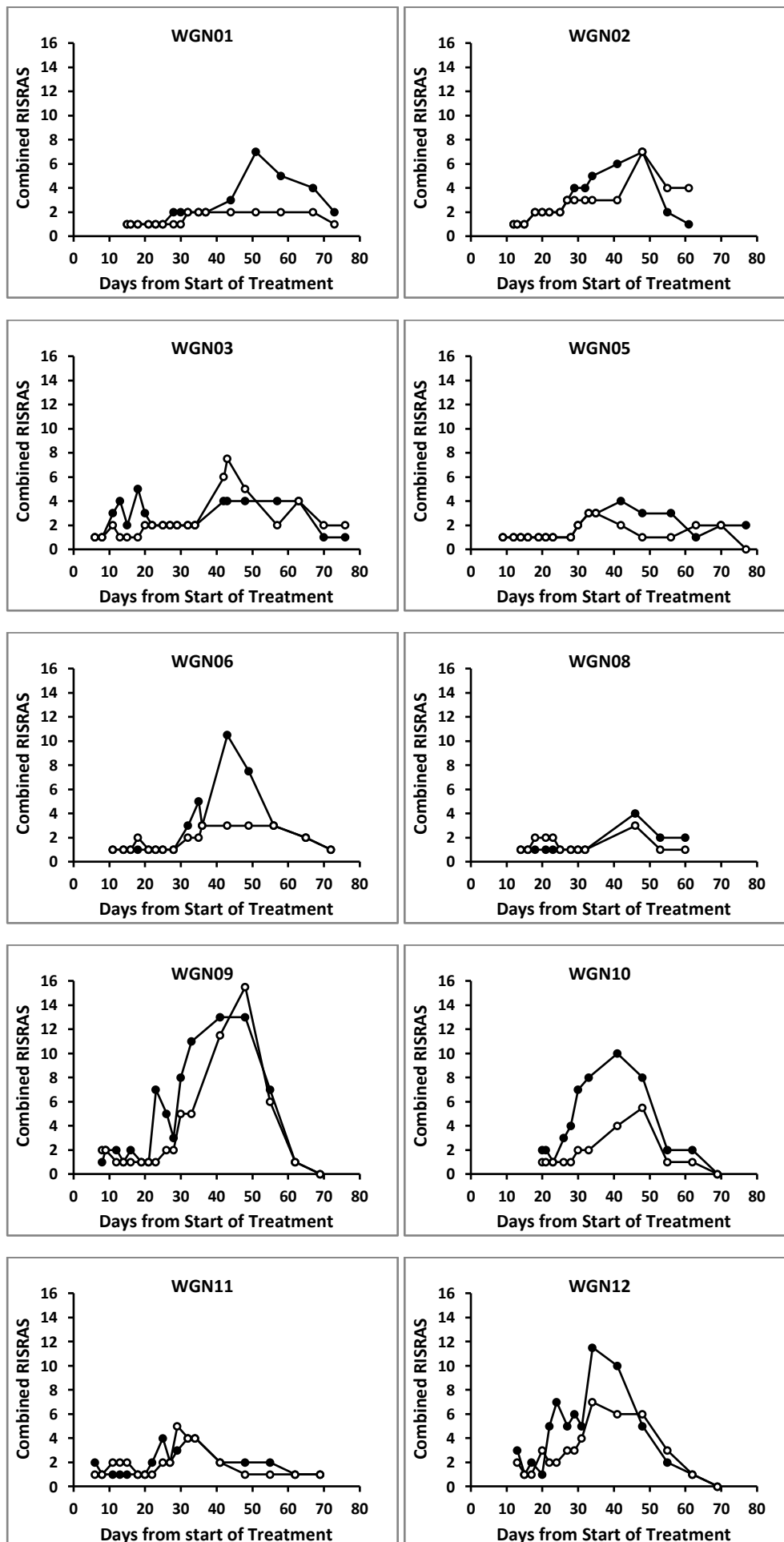


Figure 3.3 Combined RISRAS scores for individual participants.

Black symbols: Control patches. White Symbols: Mepilex Lite patches.

3.5.1. Average RISRAS Scores

The average RISRAS analysis reflects both the magnitude and duration of the acute skin reaction in each arm. All RISRAS scores for each area were summed and divided by the number of assessments, providing an average RISRAS score for each patient's intervention and control patches. Figure 3.4 illustrates the effect of Mepilex Lite on the average combined, researcher, erythema only and patient RISRAS scores. The Mepilex Lite dressings produced a statistically significant reduction in the average combined ($p=0.013$) and average patient ($p=0.031$) RISRAS scores. There was no significant reduction in the average researcher RISRAS score in this small cohort ($p=0.618$). However, when erythema only scores are compared, there is a small but statistically significant reduction in erythema under the Mepilex Lite patches ($p=0.012$). The significantly lower average combined RISRAS score in the Mepilex Lite patches appears to be heavily influenced by the patient component of the RISRAS for this cohort of patients.

3.5.2. Peak RISRAS Scores

The peak RISRAS score refers to the maximum score recorded from any assessment in each study area. For the majority of patients, the peak RISRAS score occurred at either the first or second follow-up assessment. An analysis of the peak RISRAS scores is perhaps more easily understood than the average RISRAS analysis. It is a simpler measure of severity and easier to comprehend in terms of how the reaction would manifest on the patient. Similar to the average RISRAS scores, Figure 3.5 clearly shows that the Mepilex Lite dressing significantly decreased the peak patient RISRAS score ($p=0.019$). No statistically significant difference in means was noted between patches with respect to the peak combined ($p=0.142$), researcher ($p=0.642$) and erythema only ($p=0.343$) RISRAS scores in this small cohort.

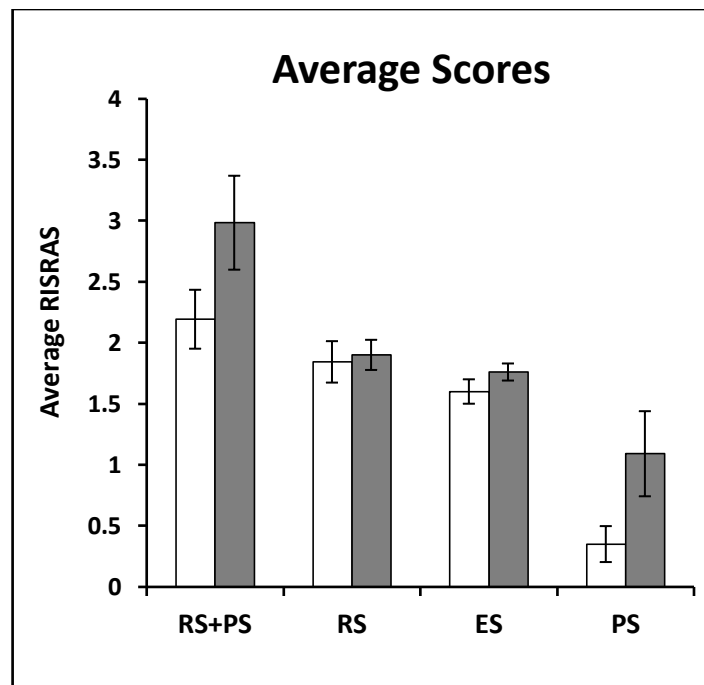


Figure 3.4 Comparison of average RISRAS scores of Mepilex Lite patches (white bars) and Control patches (grey bars).

RS+PS: Combined score. RS: Researcher Score. ES: Erythema Score. PS: Patient Score.

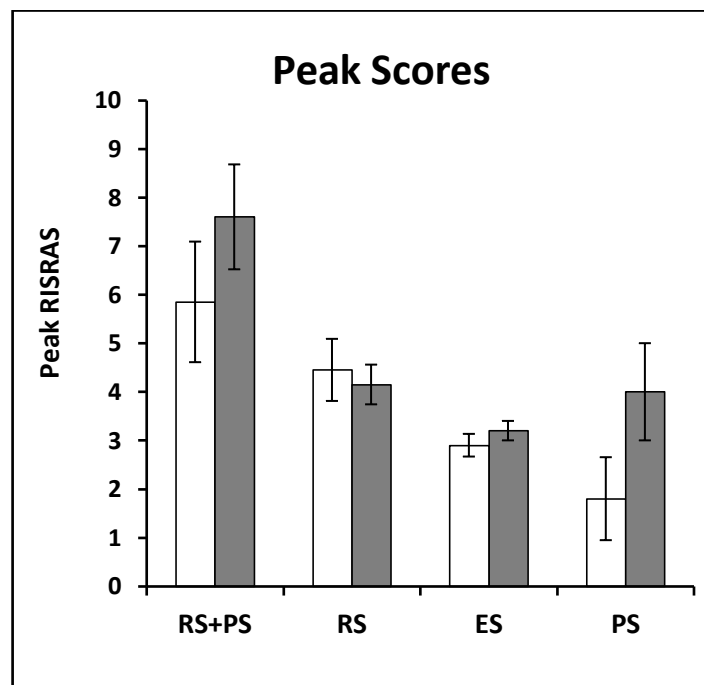


Figure 3.5 Comparison of Peak RISRAS Scores of Mepilex Lite patches (white bars) and Control patches (grey bars).

RS+PS: Combined score. RS: Researcher Score. ES: Erythema Score. PS: Patient Score.

3.6. Moist Desquamation

3.6.1. Incidence

A total of eight (80%) patients developed moist desquamation however only five (50%) of these patients developed moist desquamation in a study patch. Moist desquamation occurred in two (20%) control patches and three (30%) intervention patches (Table 3.4). In this small cohort the incidence of moist desquamation is too low to determine whether this difference is statistically significant. The area of moist desquamation represented 25% or less of the patch size in all cases.

Table 3.4 Incidence of Moist Desquamation

Participant	Control Patch	Intervention Patch	Any location
WGN01			yes
WGN02			
WGN03		yes	yes
WGN05			yes
WGN06	yes		yes
WGN08			
WGN09		yes	yes
WGN10		yes	yes
WGN11			yes
WGN12	yes		yes
Percentage (n)	20% (2)	30% (3)	80% (8)

The two patients who developed moist desquamation in their control patch were WGN06 and WGN12. The control patch for WGN06 was located near the centre of the treated area. This patient also developed moist desquamation in the axilla, which was not included in either study patch. The control patch on WGN12 partially included the axilla. The axilla was the only area which developed moist desquamation on this patient.

The three patients who developed moist desquamation in their intervention patch were WGN03, WGN09 and WGN10. The axilla was partially included in the intervention patch for both WGN03 and WGN09. Moist desquamation developed on the lateral aspect of the chest wall for WGN10. These areas of breakdown originated as a number of small blisters. The blisters were also located on other parts of the chest wall not included in the study area and therefore are highly unlikely to have been caused by the Mepilex Lite dressing.

The three patients (30%) who developed moist desquamation outside of their study area all developed it in the axilla. In all 10 patients, part of the axilla was included in the chest wall fields

(usually tangents). Seven out of the eight (87.5%) patients who presented with moist desquamation did so in the axilla.

3.6.2. Time to Onset

Data for the time to onset of moist desquamation is only available for patients where it occurred in a study patch. The mean time to onset of moist desquamation was 36.0 days (range 34 to 38 days) in the control patches and 41.3 days (range 39 to 43 days) in the intervention patches. On average, moist desquamation took 5.3 days longer to develop in the intervention patches. Due to the small cohort, this difference is not statistically significant. Only one (10%) patient (WGN12) developed moist desquamation whilst they were still receiving radiation treatment. This occurred on the final day of treatment in the patient's control patch.

3.6.3. Time to Healing

Data on the time to healing of moist desquamation is also only available for patients where moist desquamation occurred in a study patch. Time to healing was defined as the time (in days) from the development of moist desquamation until complete re-epithelisation occurred. The mean time to healing was 11 days (range 7 to 15 days) in the control patches and 12 days (range 9 to 14 days) in the intervention patches. Again this cannot be tested for statistical significance due to the small cohort and low rate of moist desquamation in the study patches.

Table 3.5 Time Course of Moist Desquamation in Control Patches

	Time to Onset (days)	Time to Healing (days)
WGN06	38	15
WGN12	34	7
Mean	36	11

Table 3.6 Time Course of Moist Desquamation in Mepilex Lite Patches

	Time to Onset (days)	Time to Healing (days)
WGN03	43	14
WGN09	39	13
WGN10	42	9
Mean	41.3	12

3.7. Exit Questionnaire

The exit questionnaire (Appendix H) was distributed to all patients at their final skin assessment. All ten (100%) patients available for RISRAS analysis completed and returned the questionnaire. The questionnaire was also completed by the one patient who withdrew from the trial (WGN07). Her views on Mepilex Lite were considered important to gain a deeper understanding of her reason(s) for withdrawal. Therefore 11 questionnaires were analysed. Responses have provided an insight into the patients' trial experience, the efficacy of Mepilex Lite and the patients' views on the advantages and disadvantages of Mepilex Lite.

3.7.1. Trial Experience

Patients were invited to comment on their trial experience. All patients (100%) identified taking part in the trial as a positive experience, including WGN07 who withdrew after wearing the dressing for only one day. Many patients commented on the perceived high standard of care they received, particularly with respect to information on skin care and the additional follow-up assessments:

"The support and communication was of a really high calibre. The follow-up was excellent all questions were answered – very professional", (WGN10).

"staff were very friendly, caring and helpful . . . taking part was easy. I was kept well informed", (WGN08).

"Yes because of the follow-up care of the burns area after I had finished R.T.", (WGN06).

Some patients acknowledged the time commitment required for the trial however they believed this extra effort was well worth it:

"The only downside was spending extra time on appointments – but this was offset by the extra care and attention!", (WGN09)

The responses also provided an insight into why the patients were willing to be involved in this trial. A number of patients alluded to a sense of altruism and a desire to help women who will receive radiation treatment for breast cancer in the future. For some it was the idea that they were involved in helping others which made their participation worthwhile:

“It is time consuming but the benefits of being involved in something that could potentially help others in their recovery is worth it”, (WGN11).

“I have no problem in taking part in trials which are a benefit to healing processes for patients”, (WGN02).

The positive experience reported by the patients is corroborated by all patients stating that they would be willing to take part in future clinical trials.

3.7.2. Efficacy of Mepilex Lite

Patients were asked their opinion on the efficacy of Mepilex Lite dressings. Nine of the ten (90%) patients who completed the trial believed that Mepilex Lite was superior to standard aqueous cream in managing their acute radiation-induced skin reaction. The patient (WGN07) who withdrew at an early stage was unable to answer this question as she “did not participate long enough” to develop an informed choice. A number of patients commented that Mepilex Lite reduced the visible extent of the skin reactions and improved the subjective experience of their reaction. In terms of their visible reaction, a reduction in redness under the dressing was commonly identified, which correlates well with the average erythema only RISRAS scores:

“could definitely see a difference with the skin”, (WGN02).

“the skin seemed less irritated under the dressing. The skin stayed a lighter red under the dressing”, (WGN08).

With regards to the subjective experience of their reaction, a reduction in itchiness beneath the dressing was described as well as a reduction in pain and burning sensation:

“my skin in general was better managed by having the patch / not as on fire as the other half also not as itchy”, (WGN10).

“I noticed a definite reduction in pain and itching on the dressing side”, (WGN09).

The one patient (WGN03) who preferred aqueous cream to Mepilex Lite commented that “the creamed area seemed to peel and heal earlier than dressing”. This patient referred to the shedding of the superficial layer of dry dead skin to expose healthy skin, which occurred as part of her healing process. The Mepilex Lite dressing appeared to delay this shedding and keep this dead skin *in situ* for

a longer period of time. For another patient (WGN05) this mechanism of Mepilex Lite was considered an advantage as the new skin more closely resembled “normal skin” when it appeared (Figure 3.6).

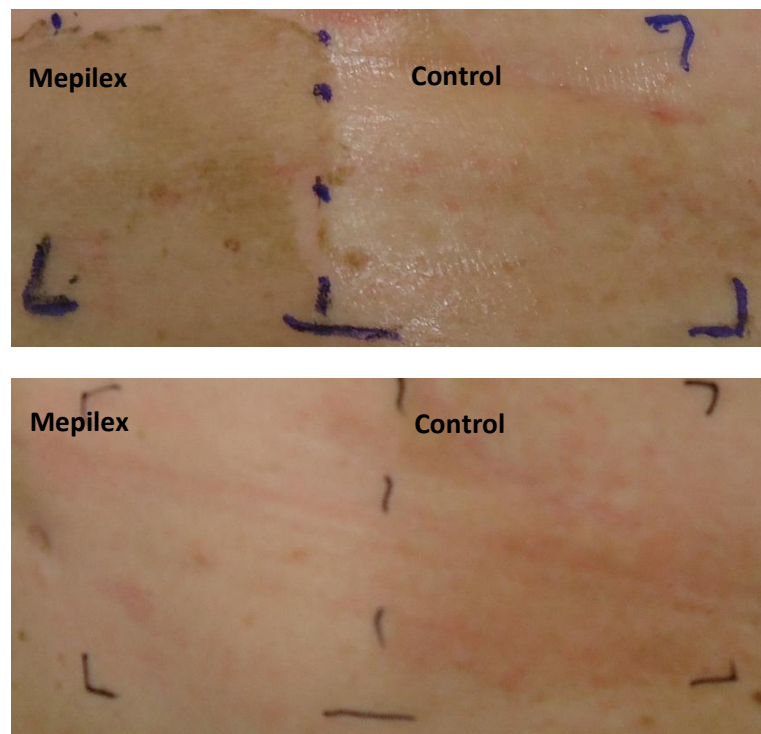


Figure 3.6 Effect of Mepilex Lite on Healing Skin

The top image shows the study area for WGN05 four weeks post radiation therapy. At this point there is a superficial layer of dry, brown, dead skin over the Mepilex Lite patch only. WGN05 stopped wearing the dressing at this point. The bottom image shows the study area six weeks post radiation therapy. The dead skin has shed leaving more “normal” appearing skin in the Mepilex Lite patch.

3.7.3. Advantages of Mepilex Lite

In addition to managing their skin reaction, patients identified two further advantages of Mepilex Lite. First, the dressing was perceived as being “comfortable” or “comforting” particularly in areas at risk of friction:

“The Mepilex formed a comfort barrier between my skin and the underwire of my bra”, (WGN11).

“comfort especially under the armpit”, (WGN03).

Another patient explained how the Mepilex Lite dressings gave her the sense that her skin was being protected:

“my skin felt more secure/safe under the dressing”, (WGN08).

The second advantage was that the dressings were “easy to use” and manage. Patients were able cut the dressings to shape and apply the dressings themselves. This is especially important in the outpatient environment of radiation therapy where patients are required to assume some degree of responsibility for self care [21]. Comments on ease of use included:

“it did not affect my daily life” “easy” “manageable”, (WGN01).

“It was very easy to apply – to my amazement it stayed in place”, (WGN06)

One patient (WGN11) who developed an area of moist desquamation outside the study area (in the axilla) was treated with the WBCC standard dressings, however she found them cumbersome and the Micropore tape used to hold the dressings in place caused a mild allergic reaction. Due to the comfort and protection she felt Mepilex Lite provided, she requested it be used over her axilla and over a number of other areas of brisk erythema, which were located outside the study patches. This patient’s experience further highlights how easily patients were able to adapt and manage the Mepilex Lite dressings to best suit their needs:

“I feel lucky to have been involved in this trial . . . I was able to use Mepilex in four other wound areas and found the healing process much better than the usual dressings given to patients. As I am allergic to most tapes I had no problems with Mepilex . . . For the underarm area, my husband and I cut the Mepilex to shape which made it easier to fit and which speed up (sic) the healing of this wound area. I used many different cut pieces on all friction areas”, (WGN11)

3.7.4. Disadvantages of Mepilex Lite

Six (54.5%) of the patients who completed the questionnaire described some degree of difficulty retaining the Mepilex Lite dressings in place, particularly under the arm. For some patients this was a significant problem was the reason one patient withdrew from the trial:

“did not adhere to skin – kept falling off”, (WGN07)

For others, the dressing becoming “unstuck” was less of an issue or was managed using Mepitac tape:

“Only occasionally it became less sticky but with clothes on holding the Mepilex in place it wasn’t a big hardship, (WGN11).

“at the beginning getting it to stay on especially when it come off for shower then off for radiation, adding the tape to secure helped but was harder to take off often pulling on skin”, (WGN03).

The only other disadvantages reported were that one patient (WGN08) experienced mild pain when removing her dressing and one patient (WGN11) reported that her skin appeared “a bit drier” but “less pink” in the Mepilex Lite patch.

4. DISCUSSION

The overarching aim of this trial was to investigate whether Mepilex Lite dressings were superior to standard care in reducing the extent of radiation-induced skin reactions in patients with breast cancer post-mastectomy. It was hypothesised that Mepilex Lite dressings would protect irradiated skin against mechanical damage caused by friction and abrasion from clothing or adjacent tissue. The soft-silicone dressings do not contain any chemical substances that could protect against radiation damage at a molecular or cellular level. This thesis analyses the results of the first ten patients who completed the trial at the Wellington Blood and Cancer Centre (WBCC).

Mepilex Lite was tested against aqueous cream, which is the current standard of care at the WBCC. Although aqueous cream has not been shown to provide any symptomatic benefit over best supportive care [44], a number of authors support the use of simple moisturisers to relieve radiation-induced skin discomfort and erythema [4, 41]. Furthermore a simple emollient, such as aqueous cream, is recommended by over 70% of radiation therapy departments in Australia and New Zealand [6]. A no treatment arm was therefore considered unethical and was not supported by the clinical staff in the department. Hydrocortisone 1% was permitted for excessive pruritus in both the intervention and control arms, as the Radiation Oncologists at the WBCC considered it an integral component of standard care. Two patients were prescribed hydrocortisone in their control patches and one patient applied it beneath their Mepilex Lite dressing.

An intra-individual comparison was used to reduce heterogeneity. Having each patient act as her own control minimised the effect of different patient and treatment related factors that have the potential to confound the results [7, 8]. Randomisation resulted in no clinical or statistical difference in radiation dose between intervention and control patches. According to Graham et al. [7], post-mastectomy irradiation provides an excellent model for an intra-individual comparison of new topical interventions for the prevention and management of acute radiation-induced skin reactions. The post-mastectomy chest wall is a uniform surface that receives a relatively homogenous dose, compared with other sites where skin reactions are common [7].

4.1. Interpretation of Results

4.1.1. RISRAS Analysis

The Modified RISRAS [21] was used to compare the outward signs (researcher component) and subjective symptoms (patient component) of acute radiation-induced skin reactions between the test patches. RISRAS was chosen as it provides a number of advantages over the more common RTOG [48] or NCI-CTC [49] scales (Appendix A). It allows for greater discrimination between small differences in the observed skin reactions, avoids the pooling together different types of reactions, indicates the size of the area of desquamation and incorporates a patient-rated component.

The average RISRAS data and the peak RISRAS data were analysed for a cohort of 10 patients at the WBCC. The average RISRAS score over the course of the trial is thought to reflect both the magnitude and duration of the reactions whereas the peak RISRAS score is an indication of the maximum severity of the reactions experienced in each arm. The researcher and patient components were analysed separately and as a combined score. The erythema score was extracted from the researcher component of the RISRAS and analysed independently to allow for comparison with the findings of the previous Mepilex Lite Trial [8].

Researcher RISRAS Scores

The recorded time to onset of erythema was consistent with the literature. The mean length of time to erythema being reported was 11.4 days. Others [3, 8] have reported that the onset of main erythema typically occurs between 10 and 14 days after the start of radiation treatment. The onset of erythema was the point at which the intervention and RISRAS assessments commenced.

Neither the average ($p=0.618$) nor the peak ($p=0.642$) analysis demonstrated a significant difference in the researcher component of the RISRAS scores between the two arms. There was a small but statistically significant improvement in the average erythema rating under Mepilex Lite dressings in this small cohort ($p=0.012$).

The reduction in average erythema scores under Mepilex Lite was supported by anecdotal reports. Both the patients and the researcher noted a visible improvement in redness under the Mepilex Lite dressings. In some cases it was possible to see exactly where the Mepilex Lite had been placed based on the redness of the skin (Figure 4.1). That there was no significant difference ($p=0.343$) between the peak erythema scores is interesting. One explanation is that Mepilex Lite had an effect on the

duration of erythema but did not reduce the maximum severity of that erythema. There is also the possibility that slight differences in redness could not always be differentiated on the erythema scale.



Figure 4.1 Reduction in Erythema under Mepilex Lite

The area of erythema is divided into two halves. To the left of the dotted line is the Mepilex Lite patch and to the right is the control patch (image taken is of patient WGN15 who is not included in this analysis but demonstrates the difference in erythema well)

Diggelmann et al. [8] investigated the effect of Mepilex Lite dressings on the extent of erythema in women who received radiation therapy to the breast. This trial reported that Mepilex Lite dressings significantly reduced the average increase in erythema ($p<0.001$) and patient ($p<0.001$) RISRAS scores. These findings are supported by the reduction in average erythema and patient scores (peak and average) documented under the Mepilex Lite dressings in the current study. Interestingly, the decrease in average erythema scores in the current trial appears smaller than that in the previous trial [8], however a direct comparison has not been performed due to the different methods of analysis used. There are a number of factors that could explain this difference:

1. The frequency of follow-up assessments was different between the two studies. The current study assessed patients weekly after treatment for up to six weeks, whereas Diggelmann et al. [8] only performed assessments one and four weeks post-radiation treatment. The majority of patients in the current study experienced their most severe reaction between one and two weeks post-treatment. It is possible that Diggelmann et al. [8] missed assessing reactions at their most severe. Differences in the severity of the reactions between these trials may account for the smaller difference in erythema scores seen in the current study. As reactions increase in severity and begin to appear deep red/purple in colour ("4" on the erythema scale); they are more likely to be given the same score.
2. The current study tested Mepilex Lite dressings on the post-mastectomy chest wall as opposed to breasts. Post-mastectomy patients tend to experience more severe skin reactions, due to the use of bolus, compared with patients who have had breast conserving surgery.
3. There is a degree of subjectivity to the RISRAS, particularly with regards to the erythema scale. It is possible that the scales were interpreted slightly differently by the evaluators in the respective trials. Some evaluators may differentiate the scoring of slight differences in erythema between study patches whereas others would score them the same.

The more favourable average erythema scores for the Mepilex Lite skin patches did not correlate with significantly better overall researcher RISRAS scores. The inclusion of dry and moist desquamation in the researcher component appears to have obscured any differences in the erythema only scores. Four patients (40%) experienced a higher average researcher RISRAS score under the Mepilex Lite dressings when compared to their control patch. Three of these patients developed moist desquamation in the intervention patch but not in the control patch. In each of these cases, the axilla was partially included in the intervention patch and may have acted as a confounding factor (discussed further in section 4.1.2). The fact that both the peak and average researcher scores failed to demonstrate a significant difference may suggest that the benefits of Mepilex Lite on the manifestation of skin reactions become less apparent in the presence of moist desquamation. However, in this cohort it appears that the small and insignificant difference in the incidence of moist desquamation between trial arms (3 control patches versus 4 intervention patches) has had a significant impact on the researcher RISRAS scores. The final analysis of all 80 patients on the larger trial may provide more meaningful results on the impact of Mepilex Lite on the development of moist desquamation and researcher RISRAS scores.

Patient RISRAS Scores

Perhaps the most significant finding in this cohort of patients is that Mepilex Lite dressings produced a large statistically significant reduction in both the average ($p=0.031$) and peak ($p=0.019$) patient RISRAS scores. The patient component of the RISRAS includes measures of subjective symptoms, such as: tenderness/discomfort/pain, itchiness, burning sensation and the effect of the skin reaction on day to day functioning. This finding also aligns with Diggelmann et al. [8] who found that Mepilex Lite reduced average patient RISRAS scores when compared with aqueous cream. Porock and Kristjanson [3] recommended that, based on a lack of empirical evidence, “the choice of topical agent should be based on the product’s ability to soothe the skin and promote comfort for the patient” (p. 153) as well as be compatible with ionising radiation. Furthermore, some patients may choose to discontinue treatment because of discomfort associated with their skin [81]. It is clear from the patient RISRAS analysis that this cohort found that the Mepilex Lite dressings promoted comfort and soothed the common symptoms associated with acute radiation-induced skin reactions. This suggests that regardless of whether Mepilex Lite is found to significantly reduce the outward signs of radiation-induced skin reactions in the larger trial, in future its use could be encouraged based on the symptomatic relief it appears to provide.

Combined RISRAS Scores

The average combined RISRAS scores showed a statistically significant improvement for the Mepilex Lite ($p=0.013$). Although the peak combined RISRAS scores demonstrated a trend towards an improvement under the Mepilex Lite, this did not reach statistical significance ($p=0.142$). It appears that both the average and peak combined scores were heavily influenced by the patient scores, which showed a large improvement with the Mepilex Lite.

Diggelmann et al. [8] only investigated the efficacy of Mepilex Lite on erythema, whereas the current trial included the full spectrum of acute radiation-induced skin reactions. Therefore, the combined RISRAS scores presented in the Diggelmann trial are only an aggregate of the erythema score and patient score. Diggelmann et al. [8] showed a statistically significant improvement in the severity of these combined RISRAS scores under the Mepilex Lite dressings compared to aqueous cream ($p<0.001$). A comparison of erythema scores plus patient RISRAS scores in the current study showed a statistically significant reduction for the intervention skin patches over the control patches (mean difference -0.90; $p=0.008$). This further suggests that the benefits of Mepilex Lite on the manifestation of skin reactions may be less apparent in the presence of moist desquamation.

4.1.2. Moist Desquamation

A secondary objective of this study was to determine whether Mepilex Lite dressings reduced the incidence of moist desquamation. It is thought that by decreasing mechanical damage, Mepilex Lite could prolong the integrity of the stratum corneum and allow basal stem cells more time to reproduce, thereby reducing the incidence of moist desquamation. Moist desquamation was selected as an endpoint as it is the most clinically relevant and significant of the acute radiation-induced skin reactions. Extensive moist desquamation can result in an infection and the suspension or early completion of radiation therapy [10, 20, 21]. This could compromise treatment outcome. Other secondary objectives were to determine whether Mepilex Lite increased the time to onset of moist desquamation compared to aqueous cream and to determine whether Mepilex Lite decreased the time to healing of moist desquamation compared to standard dressings. The standard practice for managing moist desquamation at the WBCC is a hydrogel dressing (Solosite), covered by a non-adherent wound contact layer and an absorbent pad. As there is a lack of empirical evidence regarding the management of moist desquamation, the current WBCC protocol is based on the nursing principles of moist wound care [46].

In this cohort, moist desquamation developed in two (20%) control patches and three (30%) intervention patches. However, due to size of this cohort and the low incidence of moist desquamation in the study patches, the statistical significance of these results could not be tested. Similarly, differences between the time to onset and the time to healing of moist desquamation were unable to be tested statistically. Therefore, no conclusions regarding these objectives were able to be made based on this small cohort. It is hoped that the final analysis of the results of all patients participating in this trial (which is run in four hospitals in NZ) will provide significantly relevant data.

Overall, 80% of patients in this cohort experienced moist desquamation somewhere on their chest wall. Wells and MacBride [4] state that it is difficult to estimate the number of patients who will develop moist desquamation due to a lack of systematic documentation in radiation therapy departments. Although no priori data existed at the WBCC, the incidence of moist desquamation in this cohort was higher than anticipated. Graham et al. [7] reported that only 46% percent of post-mastectomy patients developed moist desquamation in the control arm of their intra-individual comparison of a barrier film and sorbolene cream (control). The radiation therapy construct and follow-up appears similar between the two trials, although the majority of patients in the Graham trial had bolus over the scar only. All patients in the current study had bolus over the entire chest wall. As bolus increases radiation dose to the skin, this may account for the higher rate of moist

desquamation observed in this cohort. Graham et al. [7] did state that the incidence of moist desquamation reported was lower than they expected. This was attributed to the reduced extent of bolus used (1cm to scar only) in their trial compared to that used on the patients in their historical data (not stated).

The risk of developing moist desquamation appeared to have a strong correlation with the region of the chest wall included in each patch. Seven out of eight (87.5%) patients who developed moist desquamation developed it in the axilla. The axilla is prone to friction, warmth and moisture. Physical (friction) or chemical (perspiration) trauma is likely to cause further damage to the fragile skin, which has been sub-lethally damaged by the radiation, and interfere with the proliferation of stem cells in the basal layer [8]. These factors prolong the healing process and are likely to have contributed to the increased incidence of moist desquamation observed in the axilla. Porock and Kristjanson [3] also identify the axilla as the most common site of moist desquamation in their cohort of breast cancer patients receiving radiation treatment to the breast. In addition, both Graham et al. [7] and Løkkevik et al. [82] conducted intra-individual comparisons and reported a tendency for the reaction to be worse in the skin compartment including the axilla, although this trend did not reach statistical significance in either study.

A section of the axilla was encompassed in the treatment fields (tangents) for all patients; however, the axilla was not always included in the area of the chest wall that first developed erythema and therefore was not included in the study area for all patients. In cases where the axilla was included in the first erythematous area, it had equal chance of being included in the intervention or control, due to the random allocation of the Mepilex Lite. It was intended that randomisation would protect against any systematic variations in skin reactions over certain parts of the chest wall. However, randomisation did not control for differences in location in this cohort, with part of the axilla included in the intervention patch of three (30%) patients and the control patch of two (20%) patients. Because of the strong correlation between location on the chest wall and the severity of skin reactions, this was a significant confounding factor in this small cohort.

It is clear from the data that the peak radiation-induced skin reactions occurred after the patients had completed radiation treatment. Seven of the eight episodes of moist desquamation occurred during the first two weeks post-treatment. Similarly, the peak RISRAS scores were almost always observed at either the one or two week follow-up appointments. Only one patient developed moist desquamation on treatment and this manifested on the day prior to her final fraction. The fact that

the majority of radiation-induced skin reactions reach a peak after treatment is complete is well documented [7, 12, 82, 83]. Interestingly, not all trials investigating radiation-induced skin reactions include follow-up assessments during the time when reactions appear to be at their most severe [52, 58, 62, 84]. In fact, some have no follow-up whatsoever after the final fraction of radiation treatment [3, 64]. WBCC patients with moist desquamation are referred to a community nurse for follow-up skin care. Those patients whose skin looks as though it may break down post-treatment are also referred. There is currently no system in place for patients to return to the department for further skin care. The rate of moist desquamation in this cohort was higher than expected and a number of patients who did develop moist desquamation did not appear to have a significant reaction at their last on-treatment assessment. It is therefore likely that a significant number of patients who would benefit from follow-up care with a community nurse are not currently identified or referred.

The results from this cohort have helped identify a gap in service provision for patients receiving radiation treatment for breast cancer at the WBCC. It is during the first two weeks post-treatment that this group of patients are likely to need additional support and expert advice to ensure the optimal management of their skin reaction. It is especially important for moist desquamation to be managed by health professionals in order to prevent infection. Current practice appears to be inadequate and unlikely to identify all patients who would benefit from follow-up skin care. All patients should be educated on how to identify moist desquamation and informed to contact their general practitioner (GP) if it occurs. Another solution would be to refer all patients receiving radiation therapy to the chest wall to a community nurse for skin care post-treatment; however this is likely to put a substantial strain on their resources.

Cummings and Routsis [83] discuss a number of other potential solutions to this gap in service provision. One option is for a radiation therapist to provide telephone follow-up advice one to two weeks after the completion of treatment. Although this has a number of advantages, the validity of a remote assessment where the reaction cannot be viewed needs to be questioned and could result in inappropriate advice being given [83]. Another option is to introduce a radiation therapist-led follow-up clinic. This would allow all patients to have their skin reactions assessed and managed when they are at their worst. Supporting this is the fact that many patients commented that the follow-up care on the current trial helped make their participation a positive experience. The major barriers to implementing a programme such as this are the significant staffing and financial implications [83]. The implementation of follow-up care for skin reactions at the WBCC is a topic that warrants further discussion, however it is beyond the scope of this thesis.

4.1.3. Exit Questionnaire

The exit questionnaire allowed patients the opportunity to comment on different aspects of participating in the trial. Responses have provided an insight into the patients' trial experience, the efficacy of the dressing and the patients' views on the advantages and disadvantages of Mepilex Lite dressings. All patients reported that being on the trial was a positive experience, including the patient who withdrew at an early stage. Many patients alluded to a sense of altruism by expressing a desire to help others with breast cancer as a motivator for participating in the trial. An overwhelming majority (90%) of patients rated Mepilex Lite dressings as superior to standard care in managing their radiation-induced skin reaction. Only one patient preferred aqueous cream. This was because the Mepilex Lite dressings delayed the rate at which the superficial layer of dead skin cells shed during the healing process.

The efficacy of Mepilex Lite dressings was described in terms of the relief they provided to the subjective symptoms (itch, pain, burning) of the patients' reactions. The improvement in subjective symptoms correlates well with the statistically significant reduction in the patient component of the RISRAS for skin covered by Mepilex Lite dressings. This adds evidence to the conclusion that use of Mepilex Lite has a role to play in the symptomatic relief of acute radiation-induced skin reactions. In addition, patients reported that they thought the skin was less red under the Mepilex Lite dressings. This was also the prevailing view of the researcher and correlates well with the reduction in average erythema score of the skin under the Mepilex Lite dressings.

Other advantages of Mepilex Lite dressings were that they provided comfort, protection and reduced friction. These findings are supported by the limited literature available on Mepilex Lite for the management of radiation-induced skin reactions. The open diaries analysed by MacBride et al. [21] revealed that their cohort found that Mepilex Lite dressings reduced friction from clothes, bedclothes and car seat belts, which promoted comfort and improved day to day functioning. A commentary by Main et al. [81] also describes how a similar product, Mepilex Transfer, has proven beneficial to their patients' symptom management and quality of life by reducing painful irritation caused by friction and pressure.

Mepilex Lite dressings were described as being easy to use and manage. This is important in the outpatient environment where patients are required to assume some degree of responsibility for self care [21]. It is also relevant to the fact that the most severe reactions occur after the completion of radiation therapy. Further supporting these findings, Main et al. [81] reported that staff and patients

found Mepilex Transfer easy to use and custom fit for patients' needs. Additionally, MacBride et al. [21] found that patients in their study were able to apply, change and adapt Mepilex Lite dressings with ease. Another similarity with the current study is how patients adapted the dressings. Two patients in this cohort used Mepilex Lite dressings on various skin areas outside of the study area. These patients cut the dressing to shape and applied small pieces to areas of friction (e.g. from bra) or areas where the reaction was particularly painful. This mimics the "patchwork" pattern patients in the MacBride study adopted to cover affected areas and alleviate discomfort (p. E13).

The main disadvantage reported was difficulty in keeping the Mepilex Lite dressings in place, particularly under the arm. This was alluded to by over half of the cohort, although the degree of difficulty experienced varied. Again, a similar experience was reported in the case study by MacBride et al. [21] where some patients found the dressing wrinkled in awkward areas. One patient in the current study reported that her skin was drier under the Mepilex Lite dressings and another reported mild pain upon removing the dressing.

4.1.4. Initial Skin Assessment

An initial skin assessment was completed for each patient. This assessment was designed to record details of the patients' radiation construct as well as other personal and treatment related factors that may have influenced the severity of their skin reaction. A correlation analysis is planned for the final analysis of the results of all 80 patients of the larger trial to determine the effect of these variables on the likelihood of developing a severe reaction. The ability to accurately predict the likely severity of reactions would allow for a more individualised approach to skin care. Due to the size of this cohort a regression analysis was not performed. In addition, the worst area of skin reaction (the axilla) was not included in the study area for all patients. This would be a significant confounding factor as it was only the skin in the study area that was graded for severity.

4.1.5. Adverse Events

There were no serious adverse reactions to Mepilex Lite dressings in the current study. This aligns with the results of the trial by Diggelmann et al. [8], who also reported no adverse reactions to the dressing. Only MacBride et al. [21] documented that two patients on their study experienced increased itching after the dressing was applied. The researchers [21] speculated that this itchiness may have been coincidental as itching is a feature of acute radiation-induced skin reactions; however this does not explain why the symptoms settled upon removal of the Mepilex Lite. In the current

study only one patient required hydrocortisone under their Mepilex Lite dressing compared with two patients who applied hydrocortisone on their control patches. The patient who required hydrocortisone under Mepilex Lite also used it outside the study area. This suggests that skin under the Mepilex Lite dressings was no more itchy than skin in the control patches and that the dressing may have actually reduced itching in this cohort. This aligns with the significant reduction in patient RISRAS scores under Mepilex Lite and the responses to the exit questionnaire. In the current study, four patients reported some form of allergy to medical adhesives, plasters or tape. None of these patients experienced a reaction to Mepilex Lite dressings.

One patient developed folliculitis in the treatment field. The radiation oncologist responsible for her care prescribed a course of oral antibiotics (Flucloxacillin). This rash was thought to be unrelated to either the Mepilex Lite dressing or aqueous cream. Another patient developed a skin infection approximately three weeks after completing radiation treatment. This was located outside the study patches and was identified during one of the patient's follow-up assessments. This infection was treated with topical Daktacort (hydrocortisone and miconazole).

In a number of cases, the skin appeared to be slightly drier underneath the Mepilex Lite dressings. Although this was not considered an adverse event, the protocol was modified in an attempt to alleviate this. The first amendment was to encourage the use of aqueous cream as a soap substitute during showering over the entire chest wall. For the most part this was successful in reducing the obvious signs of dry skin. Application of aqueous cream underneath the Mepilex Lite was trialled, however this was unsuccessful as the dressings would not adhere to the moisturised skin. Evidently, the slight increase in dryness did not appear to concern the patients. In support of this, only one patient mentioned skin dryness as a disadvantage of Mepilex Lite on their exit questionnaire.

The original study design stipulated that patients would continue applying Mepilex Lite to the intervention patch until the acute skin reaction had fully resolved. Towards the end of the healing phase, Mepilex Lite prevented the shedding of superficial layers of dead skin (presumably by reducing friction and abrasion as per the hypothesis) to expose the healthy skin beneath. Although this mechanism is beneficial during the initial phases of the reaction and healing, keeping dead skin *in situ* over healthy skin was thought to have little benefit. The second amendment stipulated that patients who did not develop moist desquamation in the study area and scored '0' on the patient component of the RISRAS could stop applying Mepilex Lite dressings from the three week follow-up onwards. These patients would continue to use aqueous cream over both the control and

intervention patches until their skin reaction (erythema) fully resolved. Those that did develop moist desquamation at any location on the chest wall continued to apply the Mepilex Lite until the moist desquamation was full resolved (usually the third or fourth follow-up). Once patients stopped applying the Mepilex Lite, the dead skin shed quickly and the new skin beneath generally appeared lighter and more closely resembled “normal skin” (WGN05). This observation supports the hypothesis made by Graham et al. [7] that more efficient repair is likely to occur the longer the superficial skin surface remains intact.

4.2. Limitations

Sample Size

A significant limitation of this analysis is the small cohort. The final analysis will include 80 patients from four radiation therapy departments in New Zealand. As this is an Honours thesis, only the first 10 participants recruited at the WBCC have been included for analysis. The fact that a number of the RISRAS measures reached statistical significance in this small cohort suggests promising findings for the larger analysis. Due to the small sample size and the low incidence of moist desquamation in the study patches, the statistical significance of the effect of Mepilex Lite dressings on moist desquamation could not be tested. Similarly, differences between the time to onset and time to healing of moist desquamation were unable to be tested statistically.

Study Area

The main limitation of the trial design is that the study area did not include the entire treated skin area. At the first sign of erythema, the delineable erythematous patch was divided into two equal halves; one half was covered in Mepilex Lite dressings, the other managed with aqueous cream. The study area was limited to the first area of erythema for a number of reasons and follows on from the technique employed by Diggelmann et al. [8]. It was thought that the first area of erythema would experience the most severe skin reaction, receive a homogenous dose across the surface and be subject to similar external factors, such as friction. Unfortunately this does not appear to be the case in the current study.

The entire chest wall tended to develop erythema a few days after the first patch was delineated and severe skin reactions often occurred outside this area. As a result, areas of moist desquamation that developed were often excluded from the data collection and the effect of Mepilex Lite could not be tested on these areas. Another consequence is that the axilla was often either completely excluded from the study area (as it did not develop erythema first) or was partially located in only the intervention or control patch. The axilla itself was unable to be divided into two equal compartments for comparison due to its relatively small size and the difficulty in retaining a small piece of Mepilex Lite dressing in this area. The axilla was not excluded from the study due to the significance of moist desquamation in this location.

The identification of the first sign of erythema was open to interpretation. The research assistant relied on the treatment staff to monitor and identify the first sign of erythema. To confirm true

erythema the research assistant waited until a field edge was faintly visible on the skin. As discussed, the time to onset of erythema was consistent with the literature [3, 8] and is unlikely to have influenced the results.

Intra-individual Comparison

Intra-individual comparisons are common for the comparison of skin care agents in radiation therapy as the technique protects against inter-individual confounders [7, 8, 54, 58, 67, 77, 82]. Despite this advantage, it appears that the intra-individual methodology is limited if there is an uneven chance of moist desquamation occurring at different locations on the chest wall due to factors such as friction. As mentioned, the random allocation of the Mepilex Lite meant that areas with increased likelihood of developing moist desquamation (axilla) had an equal chance of being included in the intervention or control, which goes some way to ameliorate this disadvantage. Another limitation is that if moist desquamation were to occur in both the intervention and control patches, it would be difficult to manage adjacent patches differently. Potential study design solutions will be explored the next section (Chapter 4, section 4.3).

Measurements

An intrinsic limitation of the researcher component of the RISRAS is that skin evaluation is based on the subjective interpretation of the assessor. This limitation is universal to the RTOG and NCI-CTC classification systems which are commonly used in research and clinical practice. To circumvent this limitation a number of researchers have employed objective skin assessment techniques, such as reflectance spectrometry [44, 54, 58, 78], trans-epidermal water loss (TEWL) [54, 85] and photograph analysis [8, 86]. Reflectance spectroscopy provides a quantitative measure for erythema by comparing the light scattering properties of irradiated skin [4, 86]. It is limited by the fact that it can only provide a measure of erythema, is expensive and only measures erythema over a small area ($\sim 1\text{cm}^2$) of fixed points [86]. Wengström et al. [86] evaluated the use of digital photograph analysis for the assessment of radiation-induced erythema. Their results suggest that photograph analysis using Adobe Photoshop software may be a reliable way to measure skin erythema during radiation therapy. Photograph analysis was not used in the current study due to a primary interest in moist desquamation and difficulties related to standardising photographs over multiple centres. TEWL assessments provide an objective measure of the impact of irradiation on skin barrier function [85] but provide little information on the outward signs or subjective symptoms of radiation-induced skin reactions.

A pre-trial workshop was held to ensure consistent scoring of the researcher component of the RISRAS to minimise inter-scorer variability. The workshop was led by Katie Diggelmann who developed a wealth of experience using the modified RISRAS in the previous Mepilex Lite trial [8]. Thirty photographs of acute radiation-induced skin reactions were reviewed and a consensus was reached for each one. Noble-Adams [20] evaluated and validated the original RISRAS based on four clinical photographs sent to 19 experts. The inter-scorer reliability coefficients for each of the photographs were 0.72, 0.75, 0.69 and 0.64. Despite some outlying responses, the overall inter-scorer reliability can be considered satisfactory for a newly developed tool [4, 20]. A preliminary analysis has shown the average RISRAS scores for each department are consistent, which suggests that inter-scorer variability is fairly low in the current study.

Another limitation of the RISRAS is that the erythema category is predominantly applicable to Caucasian skin. This limitation is universal to other clinical assessment scales in use for acute radiation-induced skin reactions as there is no data available that describes the manifestation of erythema on darker skin [9]. Clinical experience suggests that erythema tends to manifest as increased pigmentation/tanning in non-Caucasian populations. For the non-Caucasian patients in the current study, erythema was differentiated and categorised based on the increase in pigmentation observed rather than the degree of “redness”.

Dose measurements using thermoluminescent dosimeters were unable to be performed at the WBCC due to resourcing issues. To compensate for this, surface dose estimates were made using the point dose function on the treatment planning system. These measurements are estimates based on computer modelling and therefore there is a degree of uncertainty with the measurements. The aim of the estimates was not to determine the actual dose delivered, rather, it was to ensure that there was no statistically significant difference in the relative dose received between the test patches. All patients at the Dunedin Oncology Centre will have a set of thermoluminescent dosimeter measurements for each patch. It is expected that these measurements will align with the estimates made from the treatment planning system.

The initial skin assessment was subject to recall and reporter bias. Patients were questioned about their past medical history and lifestyle. This information is subject to recall bias as some patients may struggle to remember details of their medical history. In addition, it is likely that some will under report certain lifestyle choices, such as smoking, that are deemed unhealthy. The research assistant used the patients’ oncology notes to verify appropriate data.

Blinding

In the current trial neither the patients nor the research assistant were blind to the location of the test patches. It was impossible to blind patients due to obvious differences between the dressings and aqueous cream. There is the potential that enthusiasm for the new therapy could have influenced patient responses to the patient component of the RISRAS and the exit questionnaire. This could lead to an over-estimation of the effect of Mepilex Lite dressings on acute radiation-induced skin reactions. Additionally, it is not uncommon for patients in clinical trials to report a more positive account of their symptoms as they believe it will be viewed more favourably by the researchers [87].

There is also the potential for researcher bias to influence the results. The expectation that the intervention would be better than standard care could lead to a more optimistic interpretation of the researcher component of the RISRAS. One way to introduce single-blinding into this trial would have been to have separate researchers to manage and score the patients. Patients could be instructed to remove the Mepilex Lite dressing prior to skin assessments and to not inform the researcher responsible for RISRAS scoring of the dressing allocation. This method would have had substantial resource implications for the current trial. Another option would be to take clinical photographs at each assessment and have them assessed by an offsite scorer who is blind to where the Mepilex Lite is allocated. According to Noble-Adams [20], clinical photographs have limitations regarding the ability to illustrate subtle differences between skin reactions. Photographs were found to have unrealistic colours and were unable to fully reproduce real life. In addition, photographs excluded the ability to physically examine the skin, discern moisture and assess texture [20]. Due to these limitations, clinical photographs were deemed unsuitable as a method to single-blind the current trial.

Compliance

Adherence to the trial protocol was difficult to assess. Patients were instructed to apply aqueous cream to the control patch twice a day and to cover the intervention patch with a Mepilex Lite dressing at all times, except during showering and treatment. There is no way to measure how well patients complied with these instructions and it is possible that some patients applied aqueous cream more or less often. Regardless, there is no evidence to suggest an optimal frequency for the application of aqueous cream.

A number of patients reported that the Mepilex Lite dressing would migrate from the intervention patch or fall off in bed. It is therefore possible that there were times when the dressings were partially covering the control patches. One patient (WGN04) was excluded as she was unable to place her dressing in the correct location. When this became apparent, it became standard practice to request all patients to demonstrate placement of their Mepilex Lite dressing. All other patients were able to accurately place their dressings.

One patient started using Aloe vera gel in the control patch and was instructed to stop. There is no evidence that Aloe vera is effective in preventing or minimising acute radiation-induced skin reactions in cancer patients [69]. The use of hydrocortisone 1% could influence the results. Only one patient used hydrocortisone 1% in an intervention patch whereas two patients needed it in their control patches.

4.3. Recommendations for Future Research

A number of recommendations can be suggested for future research:

1. *Scoring:* Assessing RTOG scores (in addition to RISRAS) would allow for easier comparison to other trials that have investigated acute radiation-induced skin reactions. It would also be sufficient to assess reactions once a week rather than three times a week.
2. *Blinding:* Attempts should be made to single-blind (researchers) trials investigating Mepilex Lite. This could be achieved by having separate researchers to manage the patients and score the reactions. This may be easier to manage if scores were taken only once a week.
3. *Design:*
 - a. One option is to conduct a RCT investigating the effect of Mepilex Lite on the prophylaxis and management of acute radiation-induced skin reactions in the axilla or inframammary fold only. These areas are prone to friction and are the most likely locations to develop moist desquamation [3] (for breast cancer patients). As Mepilex Lite dressings are thought to act by reducing friction, these areas are most likely to benefit. The proposed design is similar to that used by Shukla et al. [52] who investigated the effect of prophylactic beclomethasone spray on the incidence of moist desquamation in the axilla of breast cancer patients. This design would greatly reduce the chance of moist desquamation occurring outside the study area.
 - b. Another option is to conduct an intra-individual comparison and divide the entire chest wall into two equal compartments [7]. Although no part of the reaction would be excluded from analysis, the likelihood of a severe reaction remains higher at certain locations such as the axilla. Randomisation would protect against this systematic difference. Larger Mepilex Lite dressings would need to be available to cover half of the chest wall, which would be very expensive.
4. *Follow-up:* Future trials investigating acute radiation-induced skin reactions should include follow-up assessments during the first and second weeks post-treatment. This is when skin reactions are most severe.

5. *Predictive factors*: Future studies should collect data on personal and treatment factors that are thought to influence the probability of developing a severe reaction. This should be done in a standardised format across all skin care trials so that the data can be pooled and analysed together as more information becomes available. Standardised reporting of reactions and a centralised database would be required for this.

4.4. Conclusions

Acute radiation-induced skin reactions are common amongst women receiving radiation therapy for breast cancer. These reactions can be a source of significant pain, discomfort and psychological distress. Moist desquamation poses the risk of infection and can result in a treatment break, which could compromise patient outcome. There is a lack of evidence supporting the use of any particular topical agent or skin care regime in radiation therapy departments. As a result, considerable variations in skin care exist and practice is often based on historical or anecdotal evidence. Radiation therapists play a key role in the prophylaxis, monitoring and treatment of acute skin reactions. Identifying new agents that reduce the effect of these reactions will improve the standard of care radiation therapists can offer and improve the quality of life of their patients

A multicentre, open-label, randomised, intra-individual comparison of Mepilex Lite dressings versus standard care during post-mastectomy irradiation in New Zealand is being conducted. This thesis reports the results of the first 10 patients available for analysis at the Wellington Blood and Cancer Centre. It was hypothesised that Mepilex Lite dressings would protect irradiated skin against mechanical damage caused by friction and abrasion from clothing or adjacent tissue.

Mepilex Lite dressings significantly reduced the subjective symptoms of acute radiation-induced skin reactions as well as the outward signs of erythema. This was reflected in a significant overall decrease in the patient component of the RISRAS scores of the skin under the Mepilex Lite dressings. These results align with reports from the exit questionnaire and support the findings of other researchers [8, 21, 81]. An anecdotal reduction in redness was supported by lower average erythema scores under the Mepilex Lite dressings; however the decrease in peak erythema scores and researcher scores did not reach statistical significance. It is possible that the final analysis of the entire patient cohort over the four hospitals may show a statistically significant decrease in the researcher component of the RISRAS. The impact of Mepilex Lite dressings on the incidence and management of moist desquamation could not be assessed in this study, due to the small size of the cohort and the low incidence of moist desquamation in the study patches.

The fact that Mepilex Lite dressings reportedly decreased the subjective experience of acute radiation-induced skin reactions in this small, unblinded cohort is perhaps the most clinically relevant finding. Based on a lack of empirical evidence regarding the efficacy of topical skin care agents, recommendations should perhaps be based on comfort and the products ability to provide relief [3].

In some cases patients choose to discontinue treatment because of the discomfort associated with their reaction. Mepilex Lite dressings were reported to provide symptomatic relief; however as it was impossible to blind participants, some degree of participant bias cannot be excluded.

Another important finding was made concerning the incidence and development of moist desquamation at our department. Considerably more patients developed moist desquamation than was expected and in almost all cases this occurred after the completion of radiation treatment. This has helped identify a gap in service provision for patients receiving radiation treatment for breast cancer at the WBCC. Further thought must be given to the implementation of follow-up care for skin reactions.

The optimal manner in which to use Mepilex Lite dressings is yet to be determined. Perhaps the dressings are more suited for use after the patient develops subjective symptoms associated with their reaction as this is where they appeared to have the most benefit in this cohort. This experience varies widely among patients. Some will report symptoms from the onset of erythema whereas others will not complain of discomfort until moist desquamation occurs [81]. A number of patients experienced difficulty retaining the dressing in place. Although this was tolerated by most, Mepilex Lite dressings that were designed specifically to fit the axilla would be of benefit. The fact that the skin appeared slightly drier under the dressing did not appear to concern the patients.

Further research on the efficacy of Mepilex Lite dressings on the management of radiation-induced skin reactions is warranted. Trials should include the area(s) of the chest wall most likely to develop severe skin reactions and an attempt should be made to blind the researcher. Future studies would also benefit from including an RTOG assessment in addition to the RISRAS. This will allow for better comparison of results between studies. Prospective, standardised recording of data on the factors which influence skin reactions could be pooled between departments/trials and used to develop predictive models for skin reactions.

In conclusion, Mepilex Lite was found to promote comfort and reduce the subjective symptoms of acute radiation-induced skin reactions in this small cohort. There is also evidence to suggest it reduced the extent of erythema.

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APPENDIX A: Recent Trials Investigating the Prophylaxis of Acute Radiation-Induced Skin Reactions

Reference	Design	Site	Intervention/Comparison	Proposed Mechanism of Action	Outcomes Measured	Results	Additional Comments
Deodorant Use							
Theberge et al., 2009 [50]	Single-blind RCT designed to test non-inferiority n=84	Breast or Chest wall	Aluminium-free deodorant vs. no deodorant	It is thought that deodorant could create a bolus effect, irritate the skin or create scatter from metallic particles in deodorant	RTOG NCI CTCAE (v3.0)– pain & pruritus. In-house scale – sweating & discomfort.	RTOG Grade 2 (axilla): Deodorant group - 23% No deodorant group - 30% (criteria for non-inferiority $p=.019$) RTOG Grade 2 (breast): Deodorant group - 30% No deodorant group - 34% (criteria for non-inferiority $p=.049$) Similar results for other symptoms Less sweating in deodorant group ($p=0.032$)	Suggests no reason to restrict non-metallic deodorant use. Statistical power calculated to test non-inferiority of deodorant. Participants could not be blinded. Stratified based on axillary RT & adjuvant chemotherapy.
Bennett, 2009 [51]	Single-blind, RCT n=190	Breast or Chest wall	Non-metallic deodorant vs. no deodorant Deodorant made from mineral Tschermigite.	As above	RTOG- Researcher and patient assessed. Questionnaire on deodorant use.	Researcher RTOG Grade 3 (axilla): Deodorant group - 6% No deodorant group - 1% NS Researcher RTOG Grade 2 (axilla): Deodorant group - 6% No deodorant group - 4% NS	Suggests no reason to restrict non-metallic deodorant use. Study power calculated. Participants could not be blinded. Skin not assessed post-RT Not all patients in deodorant arm used deodorant.
Topical Steroids							
Shukla et al., 2006 [52]	Open label, RCT n=60	Breast or Chest wall	Beclomethasone spray vs. No skin treatment	Beclomethasone is a glucocorticoid steroid, well known for its anti-inflammatory properties.	Reaction graded in terms of erythema, dry desquamation & moist desquamation. Endpoint – moist desquamation in axilla	Moist desquamation: Beclomethasone - 13.33% No treatment - 36.66% ($p=.0369$)	Agent only applied to axilla. No patient comfort or QOL assessment. No power calculation. Patients treated on a Cobalt unit. In-house scale used.
Omidvari et al., 2007 [53]	Double-blind, RCT n=51	Post-mastectomy chest wall.	Topical Betamethasone vs. vs. vehicle emollient vs. no skin treatment	Betamethasone is a glucocorticoid steroid, well known for its anti-inflammatory properties	RTOG.	Betamethasone patients had lower mean RTOG grade but did not reach significance ($p=.055$). RTOG Grade 1 at week 3: Betamethasone – 26.3% Emollient – 64.7% No treatment – 66.7% ($p=.027$)	Study power calculated. Chest walls were treated on a 120kV superficial x-ray machine. No patient comfort or QOL assessment.

APPENDIX A: Recent Trials Investigating the Prophylaxis of Acute Radiation-Induced Skin Reactions

Topical Hyaluronic Acid (HA)

Primavera et al., 2006 [54]	Double-blind, intra-individual comparison, vehicle controlled, RCT n=20	Breast or Chest wall	MAS065D ^a (HA based cream) vs. vehicle control (emollient)	HA is a major constituent of the extracellular matrix of skin. It plays a role in facilitating tissue and wound repair by stimulating the migration of phagocytes, fibroblasts & endothelial cell proliferation. It is also a very powerful moisturiser.	NCI-CTC Skin (v2.0) Reflectance spectrophotometry. TEWL. Skin hydration using Corneometer™. Patient symptoms (itch, pain) and preference.	Mean NCI grade in MAS065D group significantly better only at week 5 ($p=.031$). Erythema score in MAS065D significantly better ($p=.004$) TEWL: NS Symptoms: NS Preference: 65% preferred MAS065D	Small sample size. No power calculated as pilot study. MAS065D randomised between left & right side of breast/chest wall. Control emollient expected to have some benefit.
Leonardi et al., 2008 [55]	Double-blind, vehicle controlled, RCT n=40	Breast	MAS065D (HA based cream) vs. vehicle control (emollient)	As above	NCI-CTC skin (v2.0). VAS- itch, burning, pain. Patient evaluation of desquamation & fatigue. Compliance.	NCI Grade >2: MAS065D - 9% Control - 88.8% ($p<.0001$) Burning in favour of MAS65D ($p=.039$) Pain, itch, dryness: NS Desquamation in favour of MAS65D ($p=.02$)	Small sample size. No power calculation Control emollient expected to have some benefit. Significantly improved skin reactions in MAS65D group.
Pardo Masferrer et al., 2010 [56]	Observational study with historical control n=98	Breast	Ureadin ^b Cream vs. Historical control	Ureadin contains 3% urea, HA and polidocanol. Urea is a natural component of the skin that functions to retain water to maintain hydration, flexibility & biomechanical processes. Polidocanol is an ethoxylated fatty alcohol with anaesthetic properties.	RTOG. VAS – patient reported symptoms of pain, itching, reddening, desquamation & QOL.	Proportion of patients who did not develop skin toxicity: Study group - 27.6% Control - 15.5% ($p<.05$) RTOG Grade >2: Study group – 21.4% Control – 40.8% ($p<.001$)	Application of study cream commenced 2-3 weeks prior to RT. Mild adverse reaction to lotion in 2 patients.

Sucalfate Based Lotions

Wells et al., 2004 [44]	Double-blind, RCT n=357	Breast, anorectal, H&N	Sucalfate cream vs. Aqueous cream vs. No cream	Mode of action for sucalfate not totally established. Thought to stimulate a number of growth factors & scavenge free radicals. Aqueous cream is a paraffin-based emollient, used to moisturise the skin.	Modified RTOG. Reflectance spectrophotometry. Likert scales – pain, pruritus, burn, sleep disturbance. Dermatology QOL index	No meaningful difference between groups at week 5. Adjusted analysis of erythema reading showed sucalfate slightly better than aqueous, but not better than no cream.	Large sample size. Study power calculated. Intention to treat analysis. Multivariate analysis identified factors that influence severity of skin reaction. Suggests application of prophylactic aqueous or sucalfate has at most a minor effect.
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APPENDIX A: Recent Trials Investigating the Prophylaxis of Acute Radiation-Induced Skin Reactions

Sucralfate Based Lotions cont.							
Falkowski et al., 2011 [58]	Open label, intra-individual comparison, non-randomised n=21	Breast	Sucralfate cream vs. No cream	As above	RTOG. Reflectance spectrophotometry.	No difference between study arms.	Small sample size. No power calculation. Non-randomised – control patch was a 5x5cm section in upper-inner quadrant. Only 6 patients developed a skin reaction during treatment. Skin toxicity not recorded post-RT No patient comfort or QOL assessment.
Trolamine (Biafine)							
Pommier et al., 2004 [62]	Single-blind, RCT n=254	Breast or Chest wall	Trolamine cream (Biafine ^c) vs. Calendula cream ^d	Trolamine is an oil-in-water emulsion with anti-inflammatory properties. Can enhance wound healing by attracting macrophages & promote production of granulation tissue. Calendula – proposed mechanism of action not described.	RTOG. VAS – pain. Interruption of treatment. Patient satisfaction.	RTOG Grade >2: Calendula - 41% Trolamine - 63% (p<.001) Treatment interruption: Calendula - 0% Trolamine - 9% Pain: in favour of Calendula (p=.03).	Large sample size. Study power calculated. Multivariate analysis identified factors that influence severity of skin reaction. Double-blinding not achieved due to obvious differences between agents. Stratified by skin phenotype. Ease of application more difficult with calendula (30%).
Elliot et al., 2006 [59]	Open label, RCT n=547	H&N	Prophylactic Trolamine (Biafine) vs. Intervention Trolamine (Biafine) vs. Standard care (differed according to dept.)	As above.	NCI-CTC Skin (v2.0) Oncology Nursing Society toxicity scoring system. Patient reported QOL. H&N Radiotherapy questionnaire. Primary endpoint - Grade 2 toxicity.	No significant benefit demonstrated. No significant difference in QOL.	Large sample size. Study power calculated. Randomisation stratified according to dose/fractionation, chemotherapy & nodal status. Intervention Trolamine commenced when symptoms started.
Matceyevsky et al., 2007 [63]	Open label, Clinical trial n=54	H&N	Solaris lotion vs. Control (Trolamine [Biafine] or Aloe vera)	Trolamine – as above Mode of action for Solaris lotion reported as being not fully elucidated.	NCI CTC (v2.0) skin	Trend towards less grade >2 skin reactions in study group but not statistically significant. More patients in the control group needed a break in treatment (p=.034).	No randomisation. Uneven sized groups. Groups were matched for age, tumour site & type of treatment. Study group also used a novel mouthwash solution. Active ingredients in Solaris & mouthwash come from the Dead Sea. No patient comfort or QOL assessment.
Gosselin et al., 2010 [60]	Double-blind, RCT n=208	Breast	Trolamine (Biafine) vs. Aquaphor ^e vs. RadiaCare ^f vs. Placebo (water spray)	Trolamine – as above Mechanism of action of other substances not reported.	RTOG. Home journal for participant self assessment.	No significant difference in minimising RTOG >2 reactions. Patients preferred Trolamine (Biafine) for ease of application & overall satisfaction.	Convenience sample. Inter-rater reliability of 0.96 prior to study initiation.

APPENDIX A: Recent Trials Investigating the Prophylaxis of Acute Radiation-Induced Skin Reactions

Trolamine (Biafine) cont.							
Abbas & Bensadoun, 2011 [61]	Open label, RCT n=30	H&N	Tromaline vs. Usual supportive care	Trolamine – as above	RTOG. Primary endpoint – Grade 3 toxicity.	RTOG Grade 3: Trolamine – 20% Control – 53.3% ($p<.01$)	Small sample size. No power calculation. No patient comfort or QOL assessment. Skin reactions assessed weekly for 4 weeks post treatment.
Other Topical Agents							
Graham et al., 2004 [7]	Open label, intra-individual comparison, RCT n=61	Post-mastectomy chest wall	No-sting barrier film (Cavilon [®]) vs. Sorbolene (control)	Barrier film thought to physically retard normal desquamation rate by reducing effects of abrasion	RTOG. Likert scales – pain, pruritus. Endpoint – moist desquamation.	RTOG area under curve: No-sting - 8.1 Sorbolene - 9.2 ($p=.005$) Moist desquamation rate: No-sting - 33% Sorbolene - 46% ($p=.096$) Pruritus was significantly reduced	Study power calculated. Intention to treat analysis. No-sting randomised between medial & lateral aspect of chest wall to protect against systematic variations in dose & other factors, such as friction.
Roper et al., 2004 [64]	Open label, RCT n=20	Breast	Theta-Cream ^h vs. Bepanthol ⁱ lotion (control)	Theta-Cream contains 3 active substances. (1) CM Glucan: promotes phagocytosis & reduces oxidative stress. (2) Hydroxypropylsilane C: decreases sensitivity to free radicals. (3) Matrixyl: stimulates collagen formation. Bepanthol is an oil-in-water emulsion containing dexpanthenol.	3 point scales used to score: erythema, desquamation, itchiness, temperature & efflorescence. Patient contentment with agent.	No significant difference between groups.	Small sample size. Skin toxicity not recorded post-treatment. One patient experienced an allergic reaction to Theta-Cream.
Vuong et al., 2004 [65]	Comparative cohort study with historical controls (Single-blind) n=15	Perineum of gynaecological or anal canal patients	Silver-leaf nylon dressing (SLND) vs. Historical controls	SLND is a non-adherent nanocrystalline silver-coated material with antimicrobial activity.	RTOG graded photos	Reduction in mean RTOG grade in favour of SLND ($p=2.73 \times 10^{-7}$).	Very small sample. 10 blind observers evaluated toxicity from photos – grades combined. Photos were available from previous cohort. Enrolled 15 consecutive patients & matched them to historical controls. No patient comfort or QOL assessment. Dressings need to remain moist. Unclear what skin care controls used.

APPENDIX A: Recent Trials Investigating the Prophylaxis of Acute Radiation-Induced Skin Reactions

Other Topical Agents cont.							
Enomoto et al., 2005 [66]	Double-blind, RCT n=30	Breast	RayGel ^l vs. Placebo gel	Aqueous based formulation containing the transdermal agents: reduced glutathione & anthocyanins. Reduced glutathione is an intracellular antioxidant. Anthocyanins regenerate spent glutathione to its reduced state to allow free-radical scavenging to continue.	RTOG grade for each of 9 breast regions.	Mean whole breast RTOG grade was 24% lower in RayGel group. NS. Worst region grade was 14% lower in RayGel group. NS.	Small sample size. No power calculation. Could be potential for cell protective compounds to be absorbed by cancer cells. Both groups also applied Aloe vera & vitamin E. No patient comfort or QOL assessment.
Mechant et al., 2007 [67]	Open label, intra-individual comparison, RCT n=45	All sites, paediatric patients	Anionic polar phospholipid-based cream (APP) vs. Aloe vera gel (dept. standard)	Phospholipids are key molecules in maintaining lamellae, lipid bi-layer & water barrier. Expected to keep skin soft, smooth, hydrated & supple.	NCI-CTC Skin (v1.0). Subject skin comfort on a 4-level scale. Dermatological assessment. Endpoint - skin care failure.	NCI grade favoured APP ($p=.004$). APP favoured for comfort variables: dry ($p=.002$), softness ($p=.057$), feels good ($p=.002$) & peely ($p=.008$). APP favoured for dermatological variables: dryness ($p=.013$), erythema ($p=.002$) & peely ($p=.008$) Skin care failure :NS	Study power calculated. Relatively low RT dose. Randomisation method unclear. No post-RT assessment until 4-6 weeks.
Wheat et al., 2007 [68]	Blinded, RCT n=20	Breast	Topical wheat grass extract vs. Sorbolene (Control)	Topical wheat grass is thought to be an immunomodulator, anti-inflammatory, substance P inhibitor, stops subcutaneous bleeding & increases fibroblastic activity of cells.	Oncology Nursing Society toxicity scoring system. Patient reported QOL.	No significant difference between groups although there was a trend towards increased time to peak incidence & improved QOL in wheat grass group.	Small sample size. Pilot study to determine whether there was sufficient evidence to justify larger trial. Unclear whether trial was single or double-blinded.

APP, anionic polar phospholipid; HA, Hyaluronic acid; H&N, head and neck; NCI-CTC, National Cancer Institute Common Toxicity Criteria; NCI-CTCAE, National Cancer Institute Common Terminology Criteria Adverse Events; NS, not significant; QOL, quality of life; RCT, randomised controlled trial; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group acute skin toxicity scale; SLND, Silver-leaf nylon dressing; VAS, Visual Analogue Scale.

^aSinclair Pharmaceuticals Ltd, Godalming, UK; ^bUSDIN, Spain; ^cGenmedix Ltd, France; ^dBoiron Ltd, Levallois-Perret, France; ^eBeiersdorf, Inc; ^fCarrington Laboratories Ltd, TX, USA; ^g3M, St. Paul, MN, USA; ^hTheraCosm, Germany; ⁱBayer Schering Pharma AG; ^jHealogica, NY, USA.

APPENDIX B: Acute Skin Toxicity Assessment Scales

RTOG Acute Radiation Morbidity Scale [48]					
Tissue	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Skin	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	Death directly related to radiation effects

RTOG, Radiation Therapy Oncology Group.

NCI CTC v4.0 [49]					
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Dermatitis Radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death

NCI CTC v4.0, National Cancer Institute Common Toxicity Criteria version 4.0.

APPENDIX C: Recent Trials Investigating the Management of Acute Radiation-Induced Skin Reactions

Reference	Design	Site	Intervention/Comparison	Proposed Mechanism of Action	Outcomes Measured	Results	Additional Comments
Topical Honey							
Moolenaar et al., 2006 [70]	Single-blind, RCT n=21 (24 areas randomised)	Breast or Chest wall	Honey gauze (HoneySoft) vs. Paraffin gauze (Unitulle)	Honey has antibacterial & anti-inflammatory activity; promotes granulation & epithelisation; & analgesic properties. Also provides a moist wound-healing environment with high nutrient content, high viscosity & high osmolality.	Primary endpoint: Closure of skin toxicity & complete healing of MD. VAS – pain, itching, irritation, malodour & general satisfaction.	Trend towards faster healing time and patient satisfaction in honey group. NS. Trend towards less pain, itching, irritation in honey population. NS.	Application of agents commenced at RTOG grade 3. Study reported in letter to editor due to early closure of trial (low accrual unlikely to result in significant difference). Scoring assessed from photographs by blinded physician. Incidence of MD in eligible patients: 4.5%
Shoma et al, 2010 [71]	RCT n=150	Breast	Sulfadiazine cream plus systematic analgesic (control) [A] vs. Sulfadiazine plus oral pentoxifylline (PTX) [B] vs. PTX plus local honey cream [C]	PTX increases blood flow & has anti-inflammatory effects. Honey – as above.	PCSA of burn. Patient symptoms – pain, burning, exudation, limitation of movement.	Increased reduction in PCSA in groups B & C at 12 weeks compared to group A ($p<.0001$) Group C had shorter duration of treatment. Significant reduction in pain in group C. Significant improvement in movement in group C.	Radiation “burn” not defined. Unclear when intervention commenced. Methodology & results not well presented & difficult to understand. Study power not calculated. No mention of blinding.
Dressings - Hydrogel							
MacMillan et al., 2007 [72]	Open label, RCT n=357	Breast, anorectal or H&N	Hydrogel (Intrasite) vs. Dry dressing (Tricotex)	Hydrogel creates a moist wound healing environment. Conforms to skin surfaces & has cooling properties.	Primary endpoint: Time to healing for MD. Modified RTOG. Likert scales– pain, itch, burn, sleep disturbance, desquamation.	Hydrogel dressings healed more slowly ($p=.03$) (HR. 0.64; 95%CI 0.42-0.99) No significant difference in comfort. 100 (28%) patients developed MD. 38% of MD occurred post-RT. Patients allocated to hydrogel more likely to use dressing ($p=.002$).	Application of agents commenced when MD present. Randomised prior to MD occurring. Second phase of a prophylaxis trial investigating sucalfate vs. aqueous vs. no cream [44]. Study power calculated. Intention to treat analysis. Stratified by anatomical area.
Gollins et al., 2008 [73]	Open label, RCT n=33	Breast, chest wall or H&N	Hydrogel vs. Gentian violet (GV)	As above.	Area of MD traced. Time to healing of desquamation. Patient withdrawal rate	Likelihood of healing greater with hydrogel (HR 7.95 ; 95% CI 2.20-26.68). At 14 days median area under curve for MD less in hydrogel group ($p=.003$). 62% of patients withdrew from GV arm (stinging & failure to heal) compared to 7% in hydrogel arm.	Application of agents commenced when MD present. Tracings taken on random days. Power calculation done Study terminated after 33 patients due to clear benefit in favour of hydrogel. Potential disadvantages of GV: dries out dermis, tissue-damaging, carcinogenic in animal studies & impairs cell migration.

APPENDIX C: Recent Trials Investigating the Management of Acute Radiation-Induced Skin Reactions

Dressings – other

Mak et al., 2005 [76]	Open label, RCT n=146	Nasopharynx	Non-adherent absorbent dressing vs. GV	GV has antifungal & antiseptic properties. Non-adherent dressings minimise trauma, protect epidermis & absorb exudate.	Primary endpoint: Healing of MD (days to complete re-epithelisation). Pain score. Mood disturbance. Neck mobility. Incidence of clinical infection.	No significant difference in wound-healing time, mood disturbance, sleep, social interaction, appearance & neck mobility. No patients developed an infection. Trend towards higher wound pain in GV group. NS.	Application of agents commenced when MD present. Randomisation occurred post-MD development. Randomisation stratified for chemotherapy. Study power calculated. Two patients withdrew due to discomfort with GV. Potential disadvantages of GV: dries out dermis, tissue-damaging, carcinogenic in animal studies & impairs cell migration.
Vavassis et al., (2008) [77]	Single-blind, intra-individual comparison n=12	H&N	Silver leaf dressing vs. Silver sulfadiazine cream (Flamazine)	Silver ions have anti-bacterial properties. Dressing is non-adherent & also provide physical barrier to infection.	RTOG.	No improvement with RTOG grade toxicity however 2/3 observers agreed on some degree of improvement with silver leaf dressing. Pain control subjectively superior on side with silver leaf dressing for 67% of patients.	Application of dressing commenced at RTOG grade >2. No mention of randomisation. Photographs taken & graded by 3 independent observers. 50% of patients asked for silver leaf dressing to be used bilaterally due to improved pain control. No comparison of time to wound healing.
MacBride et al, 2008 [21]	Case study n=16	Breast or H&N	Mepilex Lite ^a dressing.	Soft-silicone, adhesive, absorbent dressing designed to create moist wound healing environment & cause minimal trauma on removal.	Modified RISRAS. Patient diary.	Patient comfort increased with application of dressing.	Application of dressing commenced at RTOG grade 3 (confluent MD). Designed to evaluate comfort & experience of Mepilex Lite. Dressing used until reaction healed. No comparison agent. Small sample size. Two patients withdrew due to increased itching from dressing. Three patients withdrew & choose to use alternative dressings.
Diggelmann et al., 2010 [8]	Open label, intra-individual comparison, RCT n=24 (34 study areas)	Breast	Mepilex Lite dressing vs. Aqueous cream	As above Provides physical barrier to mechanical trauma & abrasion.	Endpoint: occurrence of dry desquamation. Modified RISRAS. Surface skin temperature. Dose build-up.	Mepilex Lite dressing decreased extent of erythema ($p<.001$). 71% preferred Mepilex Lite. No difference in skin surface temperature. Mepilex Lite has small bolus effect (0.5mm).	Only investigated management of erythema. Application of dressing commenced at first sign of erythema. Randomisation based on entry into trial. Small sample size. No adverse reactions.

APPENDIX C: Recent Trials Investigating the Management of Acute Radiation-Induced Skin Reactions

Topical Creams

Kirova et al., 2011 [78]	Open label, RCT	Breast or Chest wall	Hyaluronic acid ^b (HA) vs. Placebo (emollient)	HA is a major constituent of the extracellular matrix of skin. It plays a role in facilitating tissue and wound repair by stimulating the migration of phagocytes, fibroblasts & endothelial cell proliferation. It is also a very powerful moisturiser.	Endpoints: Failure (interruption of RT due to erythema) or success (disappearance of erythema after 30 days) RTOG. Colorimetric assessment with a chromameter. VAS – pain QOL – EORTC questionnaire.	No significant difference	Application of creams commenced at RTOG grade 1 dermatitis. Study power calculated. Intention to treat analysis. At baseline pain & median colorimetric score were higher in HA group. MD not included as an endpoint or measure.
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EORTC, European Organisation for Research and Treatment of Cancer; GV, gentian violet; HA, Hyaluronic acid; H&N, head and neck; MD, moist desquamation; NS, not significant; PCSA, Projected Cutaneous Surface Area; PTX, pentoxifylline; QOL, quality of life; RCT, randomised controlled trial; RISRAS, Radiation-Induced Skin Reaction Assessment Scale; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group acute skin toxicity scale; VAS, Visual Analogue Scale.

^aMölnlycke Health Care, Gothenburg, Sweden

^bAluset, Genevrier, France



Te Whare Wānanga o Ōtāgo

March, 2010

University of Otago, Wellington

Skin Reactions during Radiation Therapy after Mastectomy

PARTICIPANT INFORMATION SHEET

You are invited to participate in a clinical trial which investigates the effect of special silicon-foam dressings on skin reactions experienced by patients who receive radiation therapy for breast cancer. All participation in this research is entirely voluntary and you are free to withdraw from the study or decline any particular question or test, at any time. Please discuss your participation in this trial with family and whanau and take the time to decide whether you wish to take part in this study.

1. Why are you doing this study?

Radiation therapy to the chest wall is given with the aim of eliminating any remaining cancer cells in the area. Irradiation often causes skin reactions, which can vary from a slight reddening of the skin to severe redness and itching (which is comparable to sunburned skin). In extreme cases the skin may peel away in places, leaving the underlying tissues exposed. There are a few different ways to treat skin that has reacted to radiation therapy.

This study compares the effect of silicon-foam dressings with a conventional moisturizing cream on these skin reactions in women, receiving radiation therapy for breast cancer, who have had a previous mastectomy.

2. What does my participation in the study involve?

- Once you have been accepted into the trial you will use a moisturising cream on the irradiated area of skin. As soon as the skin becomes slightly red, a small part will be covered by a dressing by the research assistant, whilst the other parts will continue to be treated with the cream. The exact location of the dressing on the chest wall will be marked with a marker pen by the research assistant. This ensures that when the dressings are removed, they can be put back in the same place. Because the marks will fade over time, marking may need to be done several times over the course of treatment.
- During the first treatment session, small flat squares may be placed directly on your skin (see Figure 1 below). This small square contains special equipment that measures the exact amount of radiation received by your skin during each treatment.

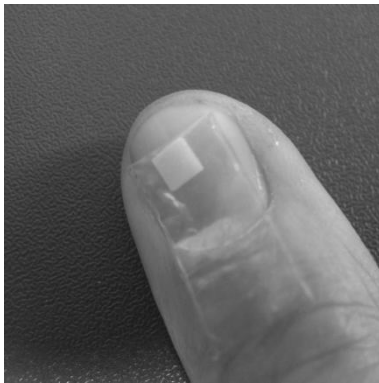


Figure 1: A small white square on the nail is the dosimeter that will be placed on your skin to measure how much radiation the skin receives each day.

- Your skin reactions will be assessed three times a week by the research assistant. The assessment form consists of a researcher part to be filled in by the research assistant and a patient part filled in by the patient.
- You will be asked to come back once a week after the completion of your radiation therapy course until your final check-up 6 weeks later (which is part of your normal hospital care) for another skin reaction assessment.

3. Are there any risks to me if I participate in this study?

Our previous skin trial showed that the dressings help alleviate the symptoms associated with radiation-induced skin reactions and that they are comfortable to wear.

- In the unlikely event of an adverse reaction to the dressings, you may stop using the dressings and treat the affected skin with the moisturising cream.
- Similarly, if the uncovered areas have a much more severe skin reaction than the covered areas, they will also be covered with the dressing.

- In the unlikely event of a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act. ACC cover is not automatic and your case will need to be assessed by ACC according to the provisions of the 2002 Injury Prevention Rehabilitation and Compensation Act. If your claim is accepted by ACC, you still might not get any compensation. This depends on a number of factors such as whether you are an earner or non-earner. ACC usually provides only partial reimbursement of costs and expenses and there may be no lump sum compensation payable. There is no cover for mental injury unless it is a result of physical injury. If you have ACC cover, generally this will affect your right to sue the investigators. If you have any questions about ACC, contact your nearest ACC office or the investigator.

4. Are there any costs involved if I participate in this study?

The only costs associated with this trial are those of attending the once a week follow-up visits. We will give you petrol vouchers to cover travel expenses. The 6 week follow-up visit is part of standard care.

5. What will you do with the information?

The information from all participants will be kept completely confidential and participant files will be stored at the University of Otago, Wellington, in a locked steel filing cabinet in the office of the Principal Investigator, Dr Patries Herst, for at least 10 years, after which time the files will be destroyed.

Only the official investigators of this study will have access to this information.

When the study is completed we will collate and analyse the information from all the participants of the study. This will tell us whether the silicon-foam dressings are better than moisturising cream in treating skin reactions. If this is the case, we aim to conduct a larger trial, and we would like to incorporate the data from this trial into a larger future study.

We anticipate that this will lead to a standardized treatment for radiation-induced skin reactions in NZ.

Reporting

- We will report on the results of this study in scientific reports and publications.
- You will be informed of the results of the study by a letter from the Principal Investigator, Dr Patries Herst

NO material will be published which can identify you personally.

You may be asked if we can use photos of parts of your chest wall to illustrate our findings. The photos will only show a small part of your chest area (see Figure 2) and no other parts of your body. You will in no way be able to be identified by these photos.

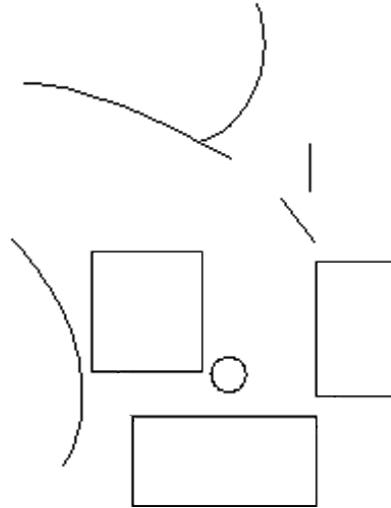


Figure 2: The patches represent the size of the dressings that are likely to be used as well as the size of the photos that may be used in reports.

6. Does the study have ethical approval?

Yes, the study has ethical approval from the Multi-region Ethics Committee.

7. Do I have to participate in this study?

No, there is absolutely no requirement to participate in the study.

8. Can I withdraw from the study if I change my mind?

If you do agree to take part, you are free to withdraw from the study at anytime, without having to give a reason and this will in no way affect your future health care.

If you wish to withdraw please contact the clinical research supervisor and advise her that you have decided to withdraw so that all information and data that have been collected about you will be entirely deleted from the database.

9. What if I have more questions or concerns about this study?

If you have any questions or concerns about your rights as a participant in this research study you can contact an independent health and disability advocate. This is a free service provided under the Health and Disability Commissioner Act. Local (03) 479 0265; Telephone: (NZ wide) 0800 555 050; Free Fax (NZ wide): 0800 2787 7678 (0800 2 SUPPORT); Email (NZ wide): advocacy@hdc.org.nz. If there is a specific Māori issue/concern please contact Linda Grennell at 0800 37 77 661

If you have any questions or concerns about your skin reactions or any other aspects of this study, at any time, please call the clinical research supervisor,

Name	Telephone
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Te Whare Wānanga o Ōtāgo

March, 2010

University of Otago, Wellington

Skin Reactions during Radiation Therapy after Mastectomy

INFORMED CONSENT

This form is to obtain your agreement to participate in our study which intends to find out whether silicon-foam dressings decrease skin reactions caused by radiation therapy treatment.

REQUEST FOR INTERPRETER

English	I wish to have an interpreter	Yes	No
Maori	E hiahia ana ahau ki tetahi kaiwhakamaori/kaiwhaka pakeha korero	Ae	Kao
Cook Island	Ka inangaro au i tetai tangata uri reo	Ae	Kare
Fijian	Au gadreva me dua e vakadewa vosa vei au	Io	Sega
Niuean	Fia manako au ke fakaaoga e taha tagata fakahokohoko kupu	E	Nakai
Samoan	Ou te mana'o ia i ai se fa'amatala upu	loe	Leai
Tokelaun	Ko au e fofou ki he tino ke fakaliliu te gagana Peletania kin a gagana o na motu o te Pahefika	loe	Leai
Tongan	Oku ou fiema'u ha fakatonulea	Io	Ikai

Informed Consent

- I have been given the opportunity to discuss my participation in this trial with family and whanau.
- I have had the opportunity to consider all the information presented and have had all my questions answered.
- I understand that my participation is completely voluntary (my choice) and that I may withdraw from the study at any time and this will in no way affect my future health care.

I would like to participate in this research study and I give consent to participating in the study assessment which includes:

- A general skin-risk assessment by the research oncology nurse.
- Regular skin reaction assessments by the research radiation therapist, which will be carried out three times a week during treatment as well as once a week after the completion of treatment until the final check-up 6 weeks after treatment. The skin assessment form has a patient part to be filled in by myself and a researcher part to be filled in by the research radiation therapist.
- Use of photographs that may be taken from parts of my chest wall for publication purposes as long as I can in no way be identified from these photos.
- The use of my information as part of a future larger trial.

I consider my ethnicity to be:

- ☐ European Pakeha
- ☐ Pakeha
- ☐ Maori
Iwi.....
Hapu.....
- ☐ Pacific Islander
.....
- ☐ Fijian
- ☐ Indian
- ☐ Asian.....
- ☐ Other (Please state)
.....

APPENDIX E: Participant Consent Form

Name:	
Signature:	
Date:	
Researchers	Dr Ptries Herst (ph 04-3855475 ext 4753; mobile 027-3483945)
Signature	
Date	

Randomisation Fax Coversheet

Mepilex Lite for Radiation-Induced Skin Reactions Trial

Date

To: Dr Ptries Herst Fax: 04-3855375
Tel: 04-3855475
Email: ptries.herst@otago.ac.nz

From:

.....

Telephone:

.....

Fax:

.....

Randomisation:

Patient Initials:

.....

Patient date of Birth:

.....

Skin Patch: Top/Left:

.....

Bottom/Right:

.....

Patient Randomization Number:

.....

Randomization Date:

.....

Randomization completed by:

.....

Signature:.....

APPENDIX G: Initial Assessment Form

Initial Skin Assessment			
	Items		Measures
Personal Construct	Age		yrs
	Weight		kg
	Separation		mm
	Smoker		yes/no; duration, packs/day
	Alcohol intake		none/less than 1, 1-3, 3-10, 10- 20, >20 drinks a week
	Nutritional Status		excellent, good, fair, poor
	Sun Exposure		frequency
	Sun Bed Use		yes/no, frequency
	Skin type		1-6 (see below)
	Co-morbidities	Diabetes	yes/no, type, controlled, duration
		High blood pressure	yes/no, controlled, duration
		Allergies	for what, medication, seriousness
		Anaemia	yes/no
		Heart Failure	yes/no
		Rheumatoid Arthritis	yes/no
		Auto-immune disorder	yes/no
		COPD	yes/no
		Hepatic failure	yes/no
	Other medications		
Genetic Construct	Ethnicity		
	Family History	relatives affected	number, level
Cancer Construct	Breast affected		
	Diagnosis		
	Tumour site		
	Stage		
	Grade		
	Size		
	Receptor Status	ER	pos/neg
		PR	pos/neg
		HER2	pos/neg
	Experienced Infection		yes/no, site
RT Construct	Machine		
	Starting Date		
	Strting Day		
	Prescription		
	Energy		
	Fields		
	Bolus		yes/no, how much
	Boost		yes/no, perscription, site
Adjuvant Therapy	Surgery		yes/no

APPENDIX G: Initial Assessment Form

			Pre/Post
			Type
			axillary dissection yes/no
	Chemotherapy		yes/no
			Pre/Post/concurrent
			Type
	Hormone Therapy		yes/no
			Pre/Post
			Type
	Alternative/Complementary		yes/no
			type
Perceived Risk	high, medium, low		

The Fitzpatrick Skin Type was developed by Dr. Thomas B. Fitzpatrick of Harvard medical school in 1975.

Determining skin type is based on: skin colour, how often and how severely they burn how well they tan

Type 1 and 2: highly susceptible to sunburn

Type 1: very fair skin (pale or milky white, possibly freckles, red/blond hair, green/blue eyes. Burn after a short time in the sun, can achieve a very light tan

Type 2: fair/very light brown skin, usually blue eyes possibly freckles. Burn after a short time in the sun, can achieve a very light tan

Type 3 and 4: Moderate susceptibility to sunburn

Type 3: ("average Caucasians") skin is slightly more brown than type 2. Can have moderate sunburn and develop light brown tan

Type 4: light brown/olive coloured skin. Ordinarily develop minor sunburn while acquiring a moderate tan. Mediterranean descend

Types 5 and 6: Minimal or No Susceptibility to Sunburn

Type 5: brown skin and can develop a dark tan while rarely burning. Hispanic, afro-american, middle eastern descend

Type 6: black skin and never burn. African descend

Mepilex Trial Exit Questionnaire

1. Was taking part in this trial a positive experience for you?

Yes/No

Please comment in the box below:

2. Do you think that the dressings were better than the cream in managing your skin reactions?

Yes/No

Please comment in the box below:

3. What were the advantages of the Mepilex dressings for you?
(such as ease of use, comfort, symptom relief and everyday-use)

APPENDIX H: Exit Questionnaire

4. What were the disadvantages of the Mepilex dressings for you?
(such as ease of use, comfort, symptom relief and everyday-use)

5. Based on your experience with this trial, would you take part in other clinical trials when appropriate?

Yes/No

Please comment in the box below:

6. Would you like the results of this trial sent to you?

Yes/No

Thank you for your participation in this trial. This valuable research would not be possible without your help.

Best of wishes for the future.