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

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ABSTRACT

Acute radiation-induced skin reactions are the most common side-effect of external beam radiation therapy ranging from changes in skin colour to dry and flaky skin, leading to moist desquamation (ulceration). Severe skin reactions compromise quality of life; however, there is currently no standard treatment. Treatment is therefore based on historical and/or anecdotal data which has resulted in substantial variation in skin care practice.

A multicentre, intra-individually controlled, randomised trial was conducted to investigate whether Mepilex Lite dressings are superior to the standard departmental 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 LTD, Göteborg, Sweden) is a thin, self-adhering, absorbent, soft silicone dressing which was hypothesised to reduce reactions by protecting the irradiated skin against mechanical damage caused by friction and abrasion from clothing or adjacent tissue. This thesis analyses the results of 13 patients recruited at the Regional Cancer Treatment Services who were a subset of the large 80 patient multicentre trial.

From the first sign of erythema on the chest wall, the erythematous patch was divided into two equal halves; one half was randomly assigned to be covered in Mepilex Lite dressings, the other to be treated with aqueous cream. Once erythema advanced to moist desquamation, skin under the control patch was dressed with dressings that were standard to the department while the intervention patch continued to be treated with Mepilex Lite dressings. The Modified Radiation-Induced Skin Reaction Assessment Scale (RISRAS) was used to assess the visual signs (researcher component) of the skin reaction while the patient component assessed symptomatic changes for at least three times a week during radiation therapy and once a week post-treatment until all reactions were resolved. An exit questionnaire was filled out by each patient upon
completion of the trial allowing them to comment on the different aspects of the trial including their experience with using the Mepilex Lite dressings.

Mepilex Lite dressings decreased the severity of skin reactions by 38% \((p=0.002)\) based on the mean combined (patients and researcher) RISRAS scores. Patient RISRAS scores heavily influenced this score, showing a decrease of 77% \((p=0.004)\) compared to the researcher scores which showed a decrease of 19% \((p=0.008)\). Analysis of the peak RISRAS scores to assess the difference in the maximum severity of the skin reactions under each arm showed a similar trend. Combined peak RISRAS showed a decrease of 43% \((p=0.005)\), with a patient component of 74% \((p=0.006)\) and a researcher component of 20% \((p=0.026)\). Analysis of moist desquamation scores alone showed a decrease in both the mean and peak RISRAS scores (38% \((p=0.04)\); 46% \((p=0.02)\) respectively) in favour of the Mepilex Lite dressings. Exit questionnaires highlighted that the silicon dressing was easy to use and comfortable to wear and most patients preferred the dressings over the cream.

The findings of this thesis demonstrates that Mepilex Lite dressings reduce the visible signs of radiation-induced acute skin reactions and cause a substantial decrease in patient discomfort and subjective symptoms.
Dedication

This thesis is dedicated to my late grandmother,

Sushila Devi Parahlad (Manjula)

Even though she did not have a formal education, she never stopped sharing her wisdom, guidance, support and encouragement for my study.
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This thesis marks the end of a long and eventful journey for which there are many people that I would like to show my immense gratitude.

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1 INTRODUCTION

Breast cancer is the most common cancer in women worldwide [1, 2], accounting for 23% (1.38 million) of the total new cancer cases throughout the world in 2008 [3]. The United Kingdom and United States of America have one of the highest incidence rates worldwide together with the rest of North America, Australia and New Zealand [1]. In New Zealand, 2713 women were diagnosed with breast cancer in the year 2008, making it the most common cancer among New Zealand women [4].

Most women with breast cancer will have some type of surgery with the primary goal of removing all cancerous tissues from the breast [5, 6]. This is often done with breast-conserving surgery called lumpectomy, where the tumour and a margin of surrounding normal tissue are removed [7]. Breast cancer that presents with gross multi-centric disease or diffuse micro-calcifications is likely to recur when treated with lumpectomy alone [8]. Therefore, a significant number of women undergo a modified radical mastectomy (see figure 1.1) for early breast cancer [9, 10]. However, even after mastectomy, loco-regional recurrence may still be a major problem [5, 10-12].

In patients who develop a loco-regional recurrence, the chest wall is the most common site with 70% of all loco-regional failures involving the chest wall [10, 12]. The mastectomy scar is the most common site for chest wall involvement [13]. The supraclavicular/infraclavicular nodes are the next most common site (10-20%), with the axilla and the internal mammary nodes being the least common [10, 12, 13]. Radiation Therapy (RT) is therefore often prescribed to patients post-mastectomy [10], with the aim to decrease loco-regional recurrence and improve overall patient survival [14].
In New Zealand, RT post-mastectomy is given through external beam therapy [7]. Either photon or electron beams are generated outside the patient by a linear accelerator and targeted at the tumour site [16]. Due to the nature of external beam therapy, radiation needs to pass through skin cells to reach the tumour, which leads to the unavoidable side-effect of radiation-induced skin reactions [17, 18].

Radiation-induced skin reactions are the most common acute side effect experienced by women receiving RT post-mastectomy [19-22]. Skin reactions differ in severity from changes in skin colour, to skin that is warm to touch, painful and itchy, to dry and flaky skin, leading to moist desquamation (ulceration) [20]. As skin reactions are currently viewed as an unavoidable part of treatment, nursing management is directed towards the palliation of skin reaction symptoms [20]. Despite skin reactions being very unpleasant and painful as well as contributing to a poor quality of life in patients, there is currently no standard treatment for radiation-induced skin reactions [21, 23].

In 2008, a pilot study was conducted in Dunedin New Zealand with a promising new range of Swedish silicon-foam skin dressings called Mepilex Lite (Mölnlycke Health ...
This trial showed that the dressings significantly reduced the severity of radiation-induced erythema when compared with standard aqueous cream [24]. However, the effect of the dressings on moist desquamation was not investigated in this trial. Moist desquamation is deemed more clinically relevant as it causes more discomfort than erythema and it carries with it the risk of infection [25]. Severe skin reactions may lead to a break in the treatment schedule which may affect tumour control and thus patient outcomes [21]. One factor that influences radiation skin damage repair is physical protection against mechanical damage [20, 24, 26]. Friction from clothes and adjacent tissue may encourage the onset of moist desquamation and slow down the repair process by impeding repair of sub-lethal damage to the stem cells in the basal layer of the epidermis [20]. In support of this, No-Sting Barrier Film from Cavelon was shown to significantly reduce the incidence of moist desquamation compared to a sorbolene cream control in 61 post-mastectomy patients treated with RT [26].

Mepilex Lite was originally designed for the treatment of burns [23]. The dressings adhere to healthy skin, do not stick to wounds nor react to chemicals in or on the skin [27, 28]. The current multicentre intra-patient controlled randomized trial aimed to determine the effect of Mepilex Lite dressings on the incidence and severity of radiation-induced moist desquamation in breast cancer patients receiving RT treatment post-mastectomy. This thesis analyses the results of a subset of 13 women treated at the Regional Cancer Treatment Services (Palmerston North Hospital).
1.1 **Skin Structure**

Skin is the largest organ of the body, accounting for 16% of the bodyweight [29]. Skin has several functions, most importantly it forms a physical barrier from the environment, allowing and limiting the inward and outward passage of water, electrolytes and various substances while providing protection against micro-organisms, ultraviolet radiation, toxic agents and mechanical insults [30]. Skin is a dynamic organ in a constant state of change, as cells of the outer layers are continuously shed and replaced by deeper cells moving up to the surface [29]. Although structurally consistent throughout the body, skin varies in thickness according to anatomical site and age of the individual [30]. There are three structural layers to the skin: the epidermis, the dermis, and subcutaneous tissues (subcutis) [29-31] (see Figure 1.2). Hair, nails, sebaceous, sweat and apocrine glands are regarded as derivatives of skin [30].

![Diagram of the different layers of the skin](image)

*Figure 1.2 Diagram of the different layers of the skin [32]*
1.2 **Acute Radiation-Induced Skin Reactions**

While the effects of radiation cannot be felt on the skin when it is administered, acute skin reactions are still the most common side-effect of RT treatment with as many as 95% of breast cancer patients experiencing some degree of reaction [33]. When ionizing radiation rays pass through a tissue cell or a cancer cell, they either interact directly with the DNA molecules that make up the chromosomes in the nucleus through ionization or indirectly by producing free radicals [34]. Both ionization and free radicals generate double stranded DNA breaks and this is the main reason that cells die after irradiation [35]. In order to eradicate the tumour cells, the beams pass through the skin to reach the tumour, damaging skin cells and causing radiation-induced skin reactions [36].

Radiation-induced skin reactions can be characterised as either acute or chronic. The outer layers of the skin are in a constant state of self-renewal [29]. Acute skin reactions to radiation occur when the skin does not produce enough new cells to replace those lost by treatment [36]. Acute skin changes usually occur within a few weeks of initiating RT and are due to the release of cytokines that cause capillary dilation, leukocyte infiltration, and localized swelling [37]. It takes time for the damage to the cells to heal, hence it usually takes 4-6 weeks after radiation treatment for the skin reactions to resolve completely [38]. Chronic (late effects) can occur anywhere from 90 days to years after completing therapy as a result of permanent damage to the dermis [31].
1.3  **Radiation–induced Acute Skin Reactions - Characteristics & Pathophysiology**

1.3.1  **Erythema**

Erythema is the first and most common radiation-induced skin reaction seen in practice [39, 40] (see figure 1.3). It is characterised as ‘reddening’ of the skin due to inflammation which is usually a result of accumulation of cells of the immune system and chemicals (cytokines) these cells release [40].

![Figure 1.3 Photograph of the chest wall of patient PLM11 showing bright erythema](image)

**Figure 1.3 Photograph of the chest wall of patient PLM11 showing bright erythema**

When skin is exposed to high doses of ionising radiation, the effects of cell death leads to the accumulation of lymphocytes in the layers of the skin and eventually to the development of erythematous skin changes [41]. Although it is extremely rare, erythema and swelling can begin within hours of initiating RT [42]. This early phase of erythema is generally transient, subsiding after 24 - 48 hours, but it may persist and resolve with time [43]. Erythematous reactions depend on numerous patient-specific parameters that are difficult to predict with high accuracy. For this reason, the minimum dose that might cause a skin change is often not expressed as a single threshold dose, but as a range of doses between 20-25 gray (Gy) [44].
1.3.2 Dry Desquamation

Dry desquamation is the second phase of acute radiation skin reactions and is characterised by dry, flaky skin that is usually itchy [19] (see figure 1.4).

![Dry desquamation](image)

**Figure 1.4 Photograph of part of the chest wall of patient PLM04 showing areas of dry desquamation**

Skin flakes occur when there is a loss of epidermal cells that break apart and are sloughed away after they are destroyed [45]. Dryness is a result of the obliteration of the sebaceous gland, found inside the hair follicle, in the dermal layer. Dry desquamation or shedding of the epidermis appears at intermediate doses of radiation (around 30Gy) [16].
1.3.3 Moist Desquamation

The most painful and difficult to manage phase of acute radiation-induced skin reactions is moist desquamation [46]. This phase is characterised by dermal cracks and fissures draining serosanguineous fluid [40] (see figure 1.5).

![Figure 1.5 Photograph of the axilla of patient PLM10 showing areas of moist desquamation](image)

Moist desquamation can occur during the final week of treatment but is usually seen and at its peak post-treatment [25, 37]. The folds of the skin tend to be predisposed to moist desquamation because radiation dose is unevenly distributed in these areas and the moist, warm folds promote skin excoriation and bacterial and fungal growth [44]. Additionally, friction resulting from movement with clothes and adjacent tissues causes excessive abrasion to the skin thereby further exacerbating moist desquamation [33]. Moist desquamation is a result of epidermal destruction and is a serious breach of skin integrity that can cause complications such as infection, pain, and limited function of the affected area in the case of the extremities. Moist desquamation appears at high-dose levels (40-60Gy) [16, 47].
1.3.4 Repair

At any one time, it is possible to see a combination of erythema, dry and moist desquamation within a single treatment field [33, 44] (see figure 1.6). For this reason, the entire area of affected skin does not heal simultaneously.

Figure 1.6 Photograph of the chest wall of patient PLM08 showing different radiation skin reactions in the same field

On average, skin reactions due to RT are usually evident within 2-4 weeks from the start of the therapy, persist for the duration of the therapy, and may require 2-6 weeks to heal after completion of treatment [20]. Healing tends to be rapid until the skin is once again intact [31]. After healing is complete, a dark, permanent pigmentation may be present in the treatment field, due to the production of melanin by the melanocytes within the epidermis in response to the ionization trauma [40]. In addition, even after healing, the skin may not be as elastic as it was before treatment [45].
1.4 Predictors of Acute radiation-induced Skin Reactions

The severity of acute skin reactions are influenced by a broad spectrum of intrinsic and extrinsic factors making both their onset and the severity difficult to predict with high accuracy [33]. Intrinsic factors are the baseline characteristics of the patient in terms of general skin condition, nutritional status, age, general health, comorbid disease and ethnicity [18]. Extrinsic factors include the dose, energy and fractionation regime of the radiation therapy treatment. The following is a theoretical framework of predictors for radiation skin reactions identified by Porock and his colleagues in 1998 [48] and developed from previous research, clinical knowledge along with experience [44].

![Figure 1.7 Risk factors for radiation-induced skin reactions adapted from Porock et al. [48] as cited by MacBride & Wells [44]](image)

Figure 1.7 Risk factors for radiation-induced skin reactions adapted from Porock et al. [48] as cited by MacBride & Wells [44]
1.4.1 Personal Construct

Personal factors are those that are unique to each individual. It is important to highlight that the various aspects of personal construct are all very closely entwined and despite the fact that they have been structured below under different subheadings, tissue repair is affected by the interplay of several of these factors at any one time [33].

Age
Epidermal turnover decreases with age resulting in extended healing times. These degenerative changes to the epidermis and dermis combined with vasculo-connective damage caused by ionizing radiation leads to an exacerbation of radiation skin reactions as age increases [33].

Weight and Breast Size
Excessive adipose tissue can compromise healing predominantly due to the reduced vascularity of adipose tissue. Excessive amount of tissue results in increased friction with movement causing excessive wear and tear on skin, causing abrasion [33]. This is often a problem with large breasted women who are more likely to experience severe skin reactions in the inframammary folds and the axilla. After mastectomy, large breasted women have a large chest wall. To deliver the prescribed radiation dose to a larger chest wall, additional beams are required due to the larger separation, which often results in a greater radiation dose to the skin. Additionally, due to increased friction and moisture in the axilla, more severe skin reactions are seen [44].

Ethnicity, Skin Type and Previous UV Exposure
A person’s ethnicity and corresponding skin colour can be indicative of the timing in which the skin reaction may be experienced [49]. Untanned (fair) skin predominantly contains melanin in the basal layer of the epidermis, whereas tanned (dark) skin contains melanin throughout the epidermis [48]. Melanin protects human skin from ultraviolet (UV) damage through its ability to absorb light over a broad spectrum [49].
Anecdotal evidence previously suggested that individuals with fair or pale skin have more severe skin reactions [33]. However, a recent study [22] has shown that high melanin content of darkly pigmented skin does not appear to be protective against ionizing radiation damage. The difference between the two groups was shown to be in the timing of the skin reactions. Fair-skinned patients were more likely to experience skin reactions during treatment whereas dark-skinned patients experienced more severe reactions post-treatment. It may be possible that skin reactions are not visualised in darkly pigmented skin until damage is more severe [22]. More severe radiation-induced skin reactions are seen in pre sun-exposed areas of the skin, suggesting additive damage [22].

**Nutritional Status and Smoking**

Optimal tissue repair requires a rich balanced diet containing all essential nutrients. Therefore, patients who are poorly nourished may heal slower [33]. Smoking limits the oxygen carrying capacity of haemoglobin [44]. Elevated carboxyhaemoglobin levels have been associated with changes to the epithelium and increased platelet stickiness [30]. Nicotine affects macrophage activity and reduces epithelialization hence delaying skin healing [44]. Smoking can also have a direct effect on nutritional status, as smokers are generally deficient in vitamins B1, B6, B12 and C [33].

**Coexisting disease**

Numerous illnesses can either directly impair with the healing process or indirectly affect the healing process through medication or reduced physical mobility, inhibiting nutritional intake and hygiene respectively. Coexisting chronic illnesses such as collagen vascular diseases, rheumatoid arthritis, lupus erythematosis, anaemia and suppression of the immune system have been identified to contribute to the severity of the radiation skin reaction [33, 44]. Diabetes mellitus has also been investigated but currently there is insufficient evidence to draw a conclusion about the role of diabetes on radiation reactions in normal tissue [33].
Stage of Disease & Seroma Aspiration

Surgery to remove larger tumours may potentially result in more trauma to the surrounding tissues and thus might increase time needed for wound healing [44]. Following surgery, patients who needed seroma aspiration are more likely to develop a severe skin reaction. Porock et al. [33] suggested that these patients are more likely to have experienced damage to their lymphatic system which may compromise wound healing during radiotherapy.

Chemotherapy & Other Drugs

Chemotherapy is often combined with radiotherapy with the aim that the two treatments work synergistically to improve loco-regional control [44]. Drugs that enhance the effects of radiation (radio-sensitizers) potentiate skin reactions [33]. Other drugs may affect radiation skin reactions by impairing with the tissue healing process.

1.4.2 Genetic Construct

Genetic factors could also make normal cells more sensitive to collateral damage by ionizing radiation [50]. Rare genetic syndromes associated with increased susceptibility to cancer and hypersensitivity to radiation include Ataxia telangiectasia, Bloom’s syndrome, Fanconi’s anaemia, retinoblastoma, Down’s syndrome, basal cell nevus syndrome and Progeria syndrome [33].

1.4.3 Radiation Construct

Radiotherapy-related factors have a significant effect on the severity of acute radiation-induced skin reactions [33].

Total dose, dose/fractionation, type and quality of the beam

The severity of skin reaction was frequently seen as an indication of total radiation dose [31]. Skin tolerance was one of the limiting factors in early RT treatment. Skin reactions are best managed by fractionation [51], which allows normal tissue to recover from sub-
lethal damage between each treatment fraction [34]. Use of photon beams from megavoltage (MV)-dedicated radiotherapy units provides increased skin sparing effect whereas the use of less-penetrating energy beams (e.g. 6MV) or less penetrating type of beam (e.g. electrons) can circumvent skin sparing [36].

Volume of the skin treated

RT-induced skin reactions in a small area heal more quickly and easily [44]. Increased discomfort or skin breakdown is experienced with a larger treatment volume. There is also a greater variation in skin dose when large areas are treated as the beam strikes the varying contours of the skin’s surface differently [33].

Beam arrangement and the use of tissue-equivalent material on skin surface

Due to the reduced amount of tissue post-mastectomy, a tangential beam arrangement is used to achieve chest wall skin irradiation. As the beam enters tangentially to the skin surface, a slightly higher dose is delivered to the tumour bed as well as to the skin [51]. Additionally, bolus material is often used to improve loco-regional control but this also increases the dose to the skin and thus increasing the severity of the skin reactions [52].
1.5 **Assessment Tools for Acute Radiation-Induced Skin Reactions**

The Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) scales [53] is probably the most widely used skin reaction scoring tool in practice and research [44]. This score uses five stages ranging from “no change” to “necrosis” (see table 1.1). Ideally, a skin assessment should be completed at baseline, prior to initiation of treatment, and reassessments should occur minimally at weekly treatment appointments [54]. The fact that RTOG/EORTC scoring starts from “No change” allows for both baseline scoring as well as weekly reassessments regardless of the onset of skin reactions. More importantly, it makes a useful distinction between faint erythema and tender, bright erythema, as well as between patchy and confluent moist desquamation.

1.5.1 **RTOG/EORTC Acute Radiation-induced Skin Reactions Scoring Criteria**

*Table 1.1 RTOG/ EORTC Acute Radiation-induced Skin Reactions Scoring Criteria adapted from Cox et al. [53] as cited by MacBride & Wells [44]*

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change over baseline</td>
<td>Follicular, faint or dull erythema; epilation; dry desquamation; decreased sweating</td>
<td>Tender or bright erythema, patchy moist desquamation; moderate oedema</td>
<td>Confluent, moist desquamation other than skinfolds, pitting oedema</td>
<td>Ulceration, haemorrhage, necrosis</td>
</tr>
</tbody>
</table>

One limitation of the RTOG scoring system is the way dry desquamation and faint erythema are scored. They are both given equal scores, which, from the patient’s point of view, may not necessarily be equal in severity. Faint erythema would also manifest differently to the appearance of dry desquamation yet the RTOG score attributes the same score to both these reactions. Similar limitations are seen in the way both bright erythema and patchy moist desquamations are given equal scores. To combat this
limitation, many researchers have modified the four criteria to generate a subdivision of score 2 and hence allowing for a distinction between the two.

Ideally, skin assessments should include an evaluation of observed physical changes as well as patient symptoms [54]. The RTOG scoring system only measures the appearance of the skin from the observer’s point of view thus giving no indication of how the patient feels. This poses a limitation on the RTOG scoring system as findings have confirmed that healthcare providers tend to underrate the severity of skin reactions when compared with patients [44].

1.5.2 Modified Radiation-Induced Skin Reaction Assessment Scale (RISRAS)

The Radiation-Induced Skin Reaction Assessment Scale (see table 1.2) was developed by Noble-Adams [55-57] in 1999 and later modified by MacBride et al. [27] in 2008. While the modified RISRAS scale uses a similar five-stage method of scoring as the RTOG/EORTC, there are marked differences between the two scoring systems. The modified RISRAS includes an evaluation of observed physical changes by the healthcare professional as well as a patient-related symptom scale. Additionally, scoring for each stage of the skin reactions is based on the percentage of skin surface affected, allowing for an accurate estimation of the area of skin affected. As mentioned earlier, it is possible to see a combination of erythema, dry and moist desquamation within a single treatment field at any one time [44]. The modified RISRAS recognizes this inconsistency in the severity of the skin reaction within a treatment area.

Whilst skin assessment tools such as the RISRAS provide useful data on the experience of patients throughout the development of skin reactions, they are open to criticism because of their lack of objectivity [44].
Table 1.2 Modified Radiation-Induced Skin Reaction Assessment Scale (RISRAS)

<table>
<thead>
<tr>
<th>RISRAS (total scores between 0 and 36)*</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Researcher Component (total scores between 0 and 24)</strong></td>
<td></td>
</tr>
<tr>
<td>Erythema (E)</td>
<td>0 Normal skin</td>
</tr>
<tr>
<td>Dry Desquamation (DD)</td>
<td>0 Normal skin</td>
</tr>
<tr>
<td>Moist Desquamation (MD)</td>
<td>0 Normal skin</td>
</tr>
<tr>
<td>Necrosis (N)</td>
<td>0 Normal skin</td>
</tr>
<tr>
<td><strong>Patient Component (total scores between 0 and 12)</strong></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>Not at all</td>
</tr>
<tr>
<td>Do you have any tenderness, discomfort or pain of your skin in the treatment area?</td>
<td>0</td>
</tr>
<tr>
<td>Does your skin in the treatment area itch?</td>
<td>0</td>
</tr>
<tr>
<td>Do you have a burning sensation of your skin in the treatment area?</td>
<td>0</td>
</tr>
<tr>
<td>To what extent has your skin reactions and your symptoms affected your day to day activities?</td>
<td>0</td>
</tr>
</tbody>
</table>

* 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.** Percentage of surface area of affected skin. Adapted from MacBríde et al. [27]
1.5.3 Objective Skin Measurements- Reflectance Spectrophotometry

Reflectance spectrophotometry is the most commonly used objective skin measurement in the clinical setting. It determines the extent of erythema in irradiated skin by measuring the blood content of the dermal microvasculature [58, 59]. As a result, it is sensitive to the vasodilatory effects that occur as a result of epithelial cell death during radiotherapy [44]. An erythema meter is held against the patient’s skin for a few seconds, and an average of 100 repeated measures of erythema is generated in a matter of seconds [60]. The degree of erythema in different areas of the treatment field can be measured, and ‘control’ measures can also be taken outside the field.

Studies that have exploited reflectance spectrophotometry as a measuring tool have demonstrated that invisible but measurable erythematous reactions occur at very low doses of radiation [58]. This may explain why some patients appear to experience skin discomfort at an earlier stage than is thought to be related to their radiotherapy. However, this method is very expensive and presents a number of practical difficulties when dealing with patients in different locations. In addition, determining which skin areas will be used for evaluation using this method is up to the researcher’s discretion, which introduces a potential source of researcher bias.
1.6 **Skin Care**

Management of radiation-induced skin reactions is a neglected area in radiation therapy practice [61]. This is primarily because radiation skin reactions are viewed as a transient and unavoidable part of treatment and therefore nursing management is often directed towards the palliation of skin reaction symptoms [20, 25].

1.6.1 **Lack of Evidence-based care**

Skin care for radiation therapy patients is a controversial subject as practices differ considerably between institutions and often also between individual practitioners [62]. There continues to be a paucity of clinical evidence to recommend any of the interventions or products that have been or are being used in clinical practice [25]. Despite numerous investigations conducted to identify skin care management, only a small number of publications have demonstrated statistically significant results [20, 21, 43]. Consequently, due to limited availability of conclusive evidence, a range of products and practices are utilised to manage patients with acute skin reactions. The management is based either on clinical trials that have shown mitigating effects of a topical agent on the severity of skin reactions, or on anecdotal and clinical experience of the radiation oncologist, radiation therapists or oncology nurses [21]. This suggests that management of skin reactions in radiation therapy departments may not always have a sound scientific basis to support the practice [63].

1.6.2 **Psychosocial Impact**

Radiation-induced skin reactions can affect quality of life by causing pain and discomfort, and by limiting daily activities [64]. The provision of skin care information to patients is essential for limiting the impact of these skin reactions [42]. The lack of consistency in information and advice between practitioners can lead to patients receiving conflicting, or even erroneous information [65]. As a result, the confusion and anxiety that patients may already be experiencing can be compounded [42]. It may also
undermine the patients’ trust in care and caregivers along with compromising prevention and healing [64].

A study conducted by D’Haese et al. [66] investigated the consensus of skin care advice given by nurses (n=67) during radiotherapy. The authors found that less than 50% of the nurses gave the same answer to one-third of the questions (33%). This was deemed to be due to lack of clear research results and, more importantly, the lack of adequate translation and implementation of these results into day-to-day practice. This confirms that there is a clear need for more research to obtain hard evidence for supporting or refuting the use of several skin care techniques.

1.6.3 General Skin Care Advice

Many general interventions and recommendations for skin care during radiation therapy are found in the literature [25]. The rationale behind these general skin care guidelines is not to prevent skin reactions, but to prevent the exacerbation of the inevitable radiation damage [20]. While individually these recommendations may not provide any supporting evidence, they are often recommended in practice based on the physicians clinical experience and the fact that they do not cause harm [25, 54]. It is important to consider that prior to making skin care recommendations to patients and family care providers, factors such as the cost, information, and ability of the patients for self-care must be considered [25].

Management of skin reaction must be flexible and change as the skin reaction progresses. The primary aim for managing dry desquamation is to alleviate patient discomfort by reducing itching and skin irritation which is often achieved by creams and lotions [21, 62, 63]. The primary aim of moist desquamation management is to prevent infection until the epidermis has regrown, using antibacterial or antifungal medication with or without soaks and dressings are often prescribed [62, 63].
1.6.4 General Skin Care advice at the Regional Cancer Treatment Services

The Regional Cancer Treatment Services provides post-mastectomy radiation therapy patients with a pamphlet outlining general skin care advice. This advice is based on routinely found guidelines in the literature and through general consensus amongst the radiation oncologists in the department. The pamphlets are given to the patients after their planning CT scan prior to treatment and read as follows

- **Bath or shower as you normally would, but be gentle with your skin in the treatment area.**
  When drying your skin in the treatment area, do not rub your skin with a towel but gently pat it dry.

- **Do not use any harsh products such as exfoliates or loofahs in the treatment area.**

- **Do not wear any tight clothing around the treatment areas as this can chafe your skin.**

- **Avoid exposing your treatment area to the sun as it is very sensitive during radiation therapy and will burn easily. You should ensure that the treated area is well protected from the sun for approximately one year after radiation. As part of good skin care, you should always ensure all of your skin is adequately protected against the sun.**

- **Before applying anything on your skin check with your radiation therapist or doctor.**

Patients are encouraged to gently wash their skin. Two clinical trials have demonstrated that washing (with or without a mild soap) has no significant negative effects on skin reactions. In addition, patients feel better about their personal hygiene [67, 68]. However, it is important to emphasize that washing needs to be gentle to avoid further trauma [67]; using the hand instead of a wash cloth [66]. The skin must then be either air-dried or pat dried using a non-abrasive towel [18, 28, 66].

Aqueous cream is preferred by almost all the radiation oncologists at the Palmerston North hospital. The use of aqueous cream on the skin has come under much scrutiny after a study published last year (2011) by Cork et al. [69] reporting that emollients containing sodium lauryl sulphate (SLS) such as aqueous cream exacerbate rather than
reduce skin barrier damage. Furthermore, in a trial conducted by Wells et al. [70], 357 patients were randomised to apply aqueous cream, sucralfate cream or no cream to investigate whether sucralfate or aqueous cream reduced acute skin toxicity during radiotherapy. Using RTOG score, reflectance spectrophotometry, patient diary card and dermatology life quality index (DLQI) to evaluate skin reactions, this study reported that there was no evidence to support the prophylactic application of either of the creams tested for the prevention of radiation skin reactions [70]. To date, these findings have not changed practice at the Regional Cancer Treatment Services.

There are other skin care guidelines that are routinely found in the literature but not outlined in the departmental pamphlet. These guidelines are as follows:

- Application of tapes and adhesives are to be discouraged to the treatment area as these can cause further injury to fragile skin [25].

- Use of cosmetic products such as perfumes, make up, or aftershaves are to be avoided in the treatment field as some products may contain traces of metal elements such as zinc or silver which could exacerbate skin reactions due to their radiation scattering effect [25, 28].

- The use of heating pads or ice packs is also not recommended to prevent thermal injury [25, 71].

- Use of electric razors for any shaving is encouraged in the treatment field to prevent further mechanical damage to the skin [25, 45].

- Patients are discouraged to go for swimming in lakes or chlorinated swimming pools or using hot tubs once dry desquamation is present or if the skin is no longer intact because of the drying and irritating potential of chemicals used in commercial pools and the risk of infections from lakes or the warm moist environment of a hot tub [25, 45].
1.6.5 Prevention of Radiation-Induced Acute Skin Reactions

This section provides an overview of twenty-one clinical trials conducted in the last ten years (since 2001), which have investigated the efficacy of various interventions for the prevention of radiation-induced acute skin reactions. The studies were difficult to compare directly as they evaluated different treatment sites (mostly breast & head and neck), used different trial designs and different treatment regimens. Compliance with intervention was also difficult to assess as this was not reported by the trial primarily because there is no completely satisfactory method of measuring compliance, in spite of the fact that it can be an important determinant of the outcome of clinical trials. The findings of these preventative trials are discussed briefly below. Please refer to Appendix G in the appendices for a more comprehensive overview of each study.

Deodorant Use

The use of deodorants within the treatment field have been of concern because they may increase the skin dose by having a bolus effect [25]. Additionally, deodorants may contain chemicals that could either directly irritate the skin or contain metallic particles that may produce scatter from the radiation which could increase the radiation dose to the skin [25, 62].

- **Two single-blinded randomised control trials conducted in 2009 compared aluminium free deodorant to no deodorant (n=84) [72] and non-metallic deodorant to no deodorant (n=190) [73] for breast cancer and chest wall patients. Both studies found that the occurrence and severity of skin toxicities did not differ between both groups, suggesting that non-metallic deodorants are safe to use with radiation therapy [72, 73].**

Topical corticosteroid agents

- **In 2002, Schmuth et al. [74] conducted a randomised double-blind study, comparing 0.5% dexamethasone cream to 0.1% methylprednisolone aceponate cream. They showed that neither creams prevented radiation-induced side effects. However, they did find that fewer patients in
the methylprednisolone group developed severe skin reactions with a score of 4 or more (p < 0.05).

- In 2006, topical beclomethasone dipropionate spray was used as prophylaxis for moist desquamation in 120 patients receiving radiation to irradiated axilla from day one of radiotherapy. A significant difference was noted in the incidence of moist desquamation in favour of the topical corticosteroid spray (13% vs. 37%, p = 0.0369) [75].

- In 2007, 51 chest wall RT patients were randomly assigned to receive either topical betamethasone 0.1, or petrolatum or nothing on their skin during RT in a study conducted by Omidvari et al. [76]. Patients receiving betamethasone had less severe grade one (RTOG) skin reactions than the other two groups which was significant only at the end of the third week (p =0.027). No significant difference was observed between the petrolatum arm and the control arm [76].

Overall, topical beclomethasone spray was the only agent that showed a decrease in both the incidence and severity of radiation-induced skin reactions.

**Non-steroidal Topical Creams**

The main source of hydration for skin is moisture from the vasculature of underlying tissues [77]. Water regulates the pliability of the epidermis, providing the rationale for the use of hydrating agents/emollients [29, 78]. Emollients reduce evaporation by forming occlusive and semi occlusive films over the skin surface, encouraging the production of moisture in the layer of epidermis beneath the film [78]. Skin hydration is achieved with lotions, creams, gels and ointments. However, there is a lack of clinical evidence to support the use of topical agents and the available research is contradictory [66].
**Aloe Vera**

Aloe Vera is a green fleshy cactus plant containing a gel that has been claimed to reduce vasoconstriction, increase leukocyte and platelet aggregation [79], activate macrophages [25] improve wound oxygenation, increase collagen formation and reduce the amount of dead tissue at the wound site [80].

- **In 2001, Olsen et al. [80]** conducted a randomised trial comparing the effect of mild soap plus Aloe Vera gel with mild soap alone in 73 cancer patients with a variety of cancer types and radiation fields, using the RTOG scale. On average, the Aloe vera gel was applied six to eight times a day. As the cumulative dose increased over time, Aloe Vera plus soap seemed to be more protective than soap alone. However, at low-dose radiotherapy, soap was reported to be better than Aloe Vera. While the authors’ concluded that Aloe Vera may show some benefit in reducing skin reactions, this statement was not supported by their tabulated data. One of the major limitations of this study was that the skin of the soap only group of patients received statistically higher doses of radiation.

- **In 2002, Heggie et al. [81]** randomised 225 breast cancer patients undergoing RT after lumpectomy or partial mastectomy to receive either 98% Aloe vera gel or aqueous cream. This was applied three times daily by the patient throughout treatment and continued two weeks after completion of radiation therapy. Aqueous cream was found to be significantly better than Aloe vera gel in reducing dry desquamation and treatment related pain as assessed by a nurse researcher. Patients in the aqueous group also experienced a greater but non-significant incidence of erythema compared with the Aloe vera group. This study did not provide any data on the production of their 2% aloe vera gel.

- **Bosley et al. [82]** conducted a controlled, intra-patient randomized trial with 45 paediatric cancer patients undergoing RT (primarily for non-Hodgkins lymphoma of the thorax) to compare an anionic polar phospholipid (APP)-based cream and an aloe vera-based gel to determine their effectiveness in preventing and treating acute radiation-induced skin
reactions. APP cream and aloe vera gel were symmetrically applied within the irradiated field after each treatment. Scores from patient-reported skin comfort variables and researcher recorded dermatologic assessments using Common Toxicity Criteria (version 1.0) showed the anionic phospholipid-based cream was significantly more effective than Aloe Vera gel in the prevention and treatment of radiation-induced dermatitis. This was an unblinded trial and similar to Heggie et al. [81], did not report the gel composition.

- Several other studies discussed in a systematic review by Richardson et al. [83] also reported that while the use of aloe vera gel is safe, it does not prevent radiation-induced skin reactions.

**Trolamine (Biafine)**

Trolamine (Biafine) is an oil-in-water emulsion with non-steroidal anti-inflammatory properties that can enhance skin healing by recruiting macrophages which facilitate the formation of granulation tissue [84].

- In 2004, Pommier et al. [84] examined the preventive effects of Biafine cream (n=128) with those of calendula ointment (n=126) in a single blinded RCT. They found that calendula ointment decreased the number of grade 2 or greater reactions (RTOG) (41% vs. 63%, $p < 0.001$), and decreased the mean maximal pain experienced ($p = 0.03$). However, the topical application of the calendula ointment was considered difficult by 30% of patients given calendula and 5% of those given trolamine, and two patients stopped using calendula because of that difficulty.

- In 2006, Elliot et al. [85] conducted a large multicentre RCT to evaluate Biafine cream in the preventative (n=166) and interventional settings (n=175) against an institutional preference (n=165), which was different for each centre. Results showed that Biafine cream did not prevent radiation-induced skin reactions. The former study stratified their patients by skin type.
• In 2008, Ribet et al. [86] conducted a small multicentre unblinded RCT in breast (n=61) and head and neck (n=8) cancer patients. Patients were randomly assigned to either Avène spring water gel (n=35) or trolamine cream (n=34) five times daily for ten weeks. The authors compared the median time to emergence of the first objective signs of radiation dermatitis in patients using Biafine or Avène thermal spring water anti-burning gel and found no significant differences between the groups [86].

• In 2010, Gosselin et al. [87] compared the effectiveness of Trolamine, Aquaphor and RadiaCare against placebo (water spray) in reducing the incidence of radiation therapy-induced skin reactions. Their double-blinded RCT involved 208 women with breast cancer who were to receive whole breast radiation therapy showed no difference between these and placebo in preventing skin reactions.

• Abbas et al. [88] conducted a study where Trolamine emulsion was compared with supportive care in 30 patients with head and neck cancer undergoing radiation therapy. Patients were randomly assigned to Trolamine emulsion every 8 h, 4 h apart from the radiotherapy session or usual supportive care. The authors reported a reduction in grade III or higher skin toxicity: 20% (3/15 cases) in the treatment group and 53.3% (8/15 cases) in the controls (p< 0.01) [88].

Although Trolamine was unable to prevent acute skin reactions in any of the above investigations, it may have some merit as a management agent.

Sucralfate Derived Creams

Sucralfate is a polysulphate compound that has been reported to have antioxidant free radical scavenging activities [89]. Free radicals are produced during the first steps of irradiation, and are responsible for destruction of malignant cells and healthy cells.

• In 2004, Wells et al. [70] investigated whether sucralfate or aqueous cream reduced acute skin toxicity during radiotherapy to the head and neck, breast or anorectal area. A total of 357
patients were randomised to apply aqueous cream, sucralfate cream or no cream to the irradiated area from day one of treatment. Skin toxicity was measured using a modified RTOG score, reflectance spectrophotometry, patient diary card and dermatology life quality index (DLQI). No consistent differences were found in the incidence and severity of skin reactions or levels of discomfort suffered by patients in each of the randomised groups [70].

- A more recent study conducted in 2011 showed that the free radical scavenging capacity of sucralfate, measured with reflectance spectrophotometry and RTOG in 21 women with breast cancer was poor. The intra-individual comparison of sucralfate cream versus no cream demonstrated that sucralfate-containing lotion did not prevent radio-induced skin reactions [90].

Both these studies showed that sucralfate lotion does not prevent radiation-induced skin reactions [70, 90]. Wells and her colleagues also did not find any evidence to support aqueous cream for the prevention of radiation skin reactions [70].

Other Topical Agents

Several other non-steroidal creams or films have been studied in the last decade to determine their effectiveness for prophylactic use of radiation skin reactions.

- In 2010, Pardo et al. [91] conducted a prospective observational study in 98 breast cancer patients to evaluate the effectiveness of “intensive use” of a hydrating lotion containing hyaluronic acid for preventing acute radiation-induced skin reactions and controlling its severity. They found that patients in the intensive group developed lower incidence of radiodermatitis (p<0.01), lower grade of toxicity (p<0.001) and lower proportion of radiodermatitis grade 2 or higher (p<0.01). The authors concluded that intensive use of the lotion halves the likelihood of developing skin reactions during radiotherapy and that if they do develop skin reactions, these will be less severe [91].
- In 2004, Roper et al. [92] conducted a very small open label study with 20 patients assigned to either the use of Θêta-Cream or Bepanthol lotion (an oil-in-water emulsion containing dexpantethenol). They found no significant differences between the groups.

- In 2004, Graham et al. [26] conducted an intra-individual comparison of Cavilon No Sting Barrier Film with sorbolene cream for the prevention of moist desquamation with breast radiation. This was a power calculated RCT with 61 patients. They reported that the incidence of moist desquamation in their cohort was 33% in the No-Sting arm and 46% in sorbolene arm (p=0.096). They found a significantly lower skin toxicity on breast areas treated in patients with No Sting Barrier Film (p = 0.005).

- Vuong et al. [93] conducted a comparative cohort study (n=15) to evaluate the value of Silver Leaf Nylon Dressing (SLND) in preventing radiation dermatitis in patients with either anal canal or gynecologic cancer. They found a reduction in the mean RTOG grade in favour of the SLND (p<0.0001).

- In a double-blinded RCT with 30 breast cancer patients, Enomoto et al. [94] compared RayGel with a placebo. In addition to RayGel or placebo, patients in both groups used Aloe Vera gel and vitamin E after radiation treatments. While they found a trend towards less severe skin reaction scores for the RayGel group, this finding was not statistically significant.

- The potential benefits of wheatgrass extract on acute skin reactions was examined in an RCT (n=) by Coulter et al. [95] who found that wheatgrass extract was no better than sorbolene cream in preventing radiation-induced skin reactions.

To conclude, while some of these clinical trials help reduce the severity of acute skin reactions with the use of various agents, very few have shown preventative promise for the incidence and severity of moist desquamation.
1.6.6 Literature Review of Management Clinical Trials

This section provides an overview of ten studies conducted in the last ten years evaluating interventions introduced from the onset of an acute skin reaction with the aim to reduce symptoms and with a strong focus on moist desquamation [63, 65]. A tabulated summary of these trials is included as Appendix G.

Hyaluronic acid

Hyaluronic acid is thought to accelerate the healing process by stimulating fibroblasts to form fibrin. Three studies appraised hyaluronidase based non-steroidal topical creams, two of these evaluated MAS065D (Xclair) which is a water-based cream with barrier-forming, hydrating, and anti-inflammatory properties.

- **In 2006, Primavera et al. [96] conducted a double blinded RCT with 20 patients acting as their own control by applying Xclair on one area and vehicle control on another area of the irradiated skin to assess the effectiveness of Xclair at managing radiation-induced skin reactions. Results showed that Xclair showed a significantly lower NCI grade of dermatitis than did areas treated with vehicle alone at week 4 of radiation \( p=0.031 \). The mean erythema scores were significantly lower in the Xclair treatment areas than in the vehicle treated areas at weeks 4, 5, and 6 of radiation \( p=0.01, 0.005, 0.03 \) respectively. No significant differences were found in pain and itch scores. Notably, 65% of patients preferred Xclair cream to the vehicle; only 10% favoured the vehicle [96].**

- **Leonardi et al. [97] conducted a double-blinded RCT in 2008, assessing the effectiveness of Xclair \( n=22 \) against that of vehicle alone \( n=18 \) in breast cancer patients receiving adjuvant radiation. The authors found a highly significant difference between the two groups in the maximum grade of radiation dermatitis \( p < 0.0001 \) after 3 weeks of radiation treatment. Their study also noted that patients in the Xclair group felt a decreased burning sensation \( p = 0.039 \) [97].**
- Hyaluronic acid was compared to a simple emollient in breast cancer patients (n=200) with grade 1–2 radio-induced dermatitis during postoperative radiotherapy [98]. Erythema occurred in 23 patients (24%) in the hyaluronic acid arm, and 32 (34%) in the emollient arm (p=0.15). There was no significant difference between hyaluronic acid and simple emollient in the treatment of acute radio-induced dermatitis. However, there was a trend towards an improvement in both pain level and skin colorimetry in the hyaluronic group [98].

While the initial two studies [96, 97] with smaller sample sizes produced statistically significant results in support of the use of Xclair as being useful in managing radiation-induced skin reactions, the large sample study [98] showed merely a trend towards an improvement in patients using hyaluronic acid.

Topical Honey
Honey may be useful as a topical antimicrobial for radiotherapy damaged skin [99]. Honey has also been shown to have anti-inflammatory characteristics [100] and may be able to scavenge free radicals produced by radiation therapy, lessening the severity of skin reactions [99].

- Moolenaar et al. [100] conducted a single-blinded study in 2006 with 21 breast or chest wall patients who were randomised to either a Honey gauze arm or a Paraffin gauze arm. The application of intervention commenced at RTOG grade 3. This study had to be closed early due to low accrual but preliminary findings showed a trend towards faster healing, patient satisfaction, and lower pain as well as reduced itching in the honey group but these were not significant.

- In 2010, Shoma et al. [101] randomly allocated breast cancer patients (n=150) into three groups each of 50 cases. Group A received standard burn treatment (control group). Group B received additional 400 mg pentoxifylline (PTX) twice daily. Group C received the same treatment as Group B with the addition of topical purified honey ointment. Patients were assessed initially and subsequently after 4 and 12 weeks, for projected coetaneous surface area
(PCSA) of burn, pain severity, limitation of movement and exudation. They found a difference in the regression of the mean PCSAs of lesions among groups B and C at 12 weeks, with reduction rates (86±61%) and (76±58%) respectively (p<0.0001). The addition of honey was associated with marked pain relieving effect and rescue of proper motion. Finally, honey was associated with shorter duration of treatment as 74% of group C patients completely recovered after 12 weeks, compared to only 54% and 36% of groups B and A in order. They concluded that the combination of PTX and honey was the best way to treat radiation-induced moist desquamation following breast conservative surgery.

Hydrogel Dressings

Hydrogels create a moist wound healing environment that may facilitate wound healing. These dressings can conform to skin surfaces, and its cooling properties may promote comfort [102].

- In 2007, Macmillan et al. [102] conducted a statistically powered RCT to evaluate the effect of a hydrogel on the time to healing of moist desquamation. Three hundred and fifty seven patients were randomised to receive simple dry dressings (Tricotex) or a hydrogel (Intrasite), with Tricotex as a secondary dressing. Moist desquamation healed more slowly in patients using hydrogel (p=0.03).

- Gollins et al. [103] performed a small (n=33) prospective RCT comparing gentian violet (GV) to a hydrogel dressing with increased healing seen in the hydrogel group (p=0.002). The study was terminated after 33 patients as a clear advantage of the hydrogel was established. However, Gentian Violet dressings were perhaps not the best control dressings as these were shown to increase pain in an RCT conducted in 2005 by Mak et al. [104].

Silver leaf Dressings

- In 2008, Vavassis et al. [105] investigated the effectiveness of silver leaf dressing in the treatment of radiation-induced dermatitis when compared with silver sulfadiazine (Flamazine) in 20 patients with an RTOG grade of 2 or more. Silver leaf dressing did not
appear to be superior to Flamazine for radiation-induced dermatitis when the RTOG grading system was used. It did, however, seem to reduce the severity of reaction within the same grade, accelerating healing, and provided improved pain control over standard treatment ($p = .035$).
1.7 Mepilex Lite Dressing

Mepilex Lite is part of a skin product line developed by the Swedish company Mölnlycke Health Care LTD, which employs Safetac Technology. This technology uses dressings that are attached to a silicon webbing which is completely inert and does not react with chemicals in or on the skin. In addition, it allows the Mepilex Lite dressings to adhere to dry surfaces, like skin, but not to moist surfaces, such as open wounds [106]. The dressing moulds to the skin’s grooves and folds, covering more skin surface and spreading peel forces on removal to prevent skin stripping [107]. The dressings seal the wound margins, minimizing the spread of exudates and the risk of maceration [108, 109]. Mepilex Lite dressings consist of a very thin layer of polyurethane foam backed by the Safetac silicone webbing [23].

Figure 1.8 Diagram of Mepilex Lite dressings

Mechanical damage to the skin is believed to retard repair of radiation damage to the skin [24]. Friction from clothes and adjacent tissue may encourage the onset of moist desquamation and slow down the repair process by impeding repair of sub-lethal damage to stem cells in the basal layer of the epidermis [20]. Dressings provide the physical protection needed against mechanical damage and stop premature loss of skin integrity during the healing process [20, 24, 26]. Graham et al. [26] hypothesized that reducing surface attrition owing to friction was the reason that No-Sting Barrier Film
significantly reduced the incidence of moist desquamation compared to a sorbolene control in 61 post-mastectomy patients treated with RT [26].

Figure 1.9 Diagram showing the non-stripping characteristics of Safetac technology [23]

- In 2008, a small case study (n=16) evaluated patient comfort when using Mepilex Lite in the management of dry and moist desquamation including safety, tolerance, and influence on healing. Assessment tools included RTOG and RISRAS as well as digital photographs taken at each weekly visit. Patients completed the RISRAS, daily diary cards, and open diaries for quantitative and qualitative evaluation. Patients reported the dressing to be conformable, soothing and cooling as well as less painful during dressing changes. They were easy to lift and adjusted without loss of adherent properties. The dressing had no negative effect on wound healing [27].

- Diggelmann and colleagues [24] conducted a small clinical in-patient controlled pilot study of 23 patients investigating the effect of Mepilex Lite dressings in reducing radiation-induced erythema in women with breast cancer. They measured the extent of skin reactions using RISRAS and photographs and found that Mepilex Lite dressings significantly reduced the severity of radiation-induced erythema compared with standard aqueous cream (p < 0.001) [24]. This trial did not study the effects of these dressings on moist desquamation.
1.8 **Aims & Objectives**

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 radiation treatment for breast cancer post-mastectomy.

**Hypothesis**

Mepilex Lite dressings decrease the incidence and extent of radiation-induced skin reactions in women receiving RT for breast cancer post-mastectomy.

**Primary Objective**

- To determine whether Mepilex Lite dressings reduce the incidence and extent of moist desquamation.

**Secondary Objectives**

- 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**

- Incidence and extent of moist desquamation

**Secondary Endpoints**

- Time of onset to moist desquamation
- Time to healing
2 METHODOLOGY

This thesis project was part of a trial designed as a multicentre, open label clinical trial that performed an intra-individual comparison of Mepilex Lite dressings to control aqueous cream in post mastectomy radiation therapy patients. Being a multicentre study, ethics approval was gained from the Multi-region Ethics committee in April of 2010 and May of 2011 (MEC/10/04/033). This study was also registered with the Australia New Zealand Clinical Trials Registry (ACTRN12611000718943). Participants were recruited in New Zealand from three North Island radiation therapy centres located in Auckland, Palmerston North and Wellington and one South Island centre located in Dunedin. This thesis analyses the results of 13 patients recruited at the Regional Cancer Treatment Services in Palmerston North Hospital who were a subset of the large 80 patient multicentre trial.

**Participant Numbers**

The pilot study conducted by Diggelmann et al. [24] showed that Mepilex Lite dressings reduced the incidence of moist desquamation from 24% to 15% in 34 paired skin patches in relatively low risk areas. The current trial focuses on the chest wall of post-mastectomy women. Although the incidence of moist desquamation is thought to be higher in these patients, the incidence in New Zealand needs to be determined before power calculations for the larger trial can be made. This study aims to recruit a total of 80 patients over four centres. A previous skin trial on post-mastectomy patients conducted by Graham et al. [26] in Australia on 61 patients reached significance and hence we are confident that this study will give us enough information to adequately power a larger multinational trial.

**Inclusion Criteria**

All women aged 18 years or over receiving post-mastectomy RT for breast cancer were eligible.
Exclusion Criteria

Women with previous RT to the chest wall or metastatic disease, breast reconstruction surgery, impaired mobility, and Karnofsky performance status scores of less than 70 were excluded. Women who were unable to come back to the department for additional skin assessments once a week post treatment until the final check-up at 6 weeks were also excluded.

Description of RT Treatment

Adjuvant radiation therapy was prescribed post-mastectomy at 50Gy in 25 fractions (treatments) or at a biologically equivalent dose at the treating clinician’s discretion. There are several regimens in common use but intra-patient comparison negates this variable. In Palmerston North, chest wall patients were treated in the supine position with their arms up on a wingboard. Treatment was administered with a mixture of 6 megavoltage (MV) and 15MV tangential photon beams with segments. Usually a 0.3cm or a 0.5cm bolus was prescribed to the chest wall. Depending on the nodal status, some patients received treatment to the supraclavicular and axillary nodes with an anterior posterior beam arrangement. Patients received treatment on all working days.

Informed Consent

Each patient was first approached about the trial by the research assistant (the author) after their planning computed tomography (CT) scan. They were provided with a written copy of the “Participation Information Sheet” (Appendix A) and the information in this sheet was verbally discussed with them. The patients then got a chance to ask any questions that they had at the time. There is a minimum two week window between the planning CT scan and the commencement of treatment during which patients took the information sheet home and were encouraged to read the information again. At the first radiation treatment appointment, the patients were approached again and any questions or queries the patient had were answered before informed consent was gained. Consent was gained through the patient signing the “Informed Consent” (Appendix B)
document. The RO of each consenting patient also signed the informed consent. To ensure all radiation therapists and radiation oncology nurses treating the patient were aware of the patient’s enrolment in the trial; a note was added into the patients’ Mosaix folder with this information. Additionally, alerts were placed on the patients’ schedule reminding the treatment staff to check for signs of erythema and informing the research assistant (the author).

**Randomisation and Intra-individual Comparisons**

Using intra-patient controls circumvents the confounding patient-related and treatment-related factors. Randomisation circumvents the effect of small dose differences between the dressed and undressed patches.

![Randomisation Sheet](image)

**Figure 2.1 Showing randomisation for PLM06**

After gaining informed consent, a randomisation coversheet (see figure 2.1 & Appendix D) was completed and sent to the principal investigator Dr Patries Herst at the
University of Otago in Wellington for randomisation using pre-prepared computer generated charts which were created by a biostatistician at the University of Otago in Wellington.

At the first sign of erythema, the erythematous patch of skin was divided into two halves: either superior and inferior halves or medial and lateral halves. One half of the skin was covered with Mepilex dressing while the other half was treated with control aqueous cream. Which half received the Mepilex Lite dressing was determined by referring to the randomisation cover sheet. The following is an example of the two ways in which the patient PLM06 with the randomisation sheet in figure 2.1 could be randomised:

Figure 2.2 Demonstrating the two possible ways the study patches could be allocated based on the randomisation in Figure 2.1

**Blinding**
The study was an open label clinical trial where both the researchers and participants knew which patch of the skin was treated with the control and which patch was treated with Mepilex Lite dressing. Due to the nature of the study, the patients could not be blinded as the dressings and aqueous cream are noticeably different. The research
assistant (the author) who divided the skin and visually scored the skin reaction was also not blinded to the treatment allocation.

**Serious adverse events and Discontinuation**

The foam and silicone webbing in the Mepilex Lite dressings do not contain any chemicals and therefore do not react with the skin. In previous studies, none of the patients had experienced a serious adverse event related to the dressings [24, 27]. However, if itching or any other side effects of an unknown nature was to occur, the dressing was to be removed and the patient’s skin was to be treated with aqueous cream or as recommended by the treating clinician.
2.1 **Trial Procedure**

The patch of skin showing the first sign of erythema on the post-mastectomy chest wall was divided into two equal halves and the Mepilex Lite dressing was allocated as per randomisation sheet. Although patients could develop more than one area of erythema; only the first erythematous area was considered for randomisation to facilitate statistical analysis. Any additional erythematous skin patches were treated with local standard care. General skin care guidelines were provided to each patient as outlined in section 1.6.4.

2.1.1 **Treatment Arm**

Each patient was given Mepilex Lite dressings pre-cut to the size of their treatment skin patch and were directed to change the dressings when necessary (approximately every 2-3 days). The placement of the Mepilex according to the patient’s randomisation was discussed with the patient. Patients received the dressings free of charge. The exact position of the dressings was indicated with a semi-permanent marker pen so that when the dressings were removed during treatment or before showering, they could be reapplied in exactly the same location. The dressings were only re-applied after showering if they were clean and maintained their adhesiveness.

Although Diggelmann et al. [24] reported that RT can be administered through the dressings, they did have a very small bolus effect. Additionally, depending on the position of the Mepilex Lite, the dressings could obscure treatment positioning tattoos in some patients. Therefore, all dressings were removed before radiation treatment. Mepilex Lite dressings were used from the first sign of erythema throughout the duration of RT treatment and continued after completion of RT treatment until the skin reactions were fully resolved. From the onset of moist desquamation, the dressings were replaced daily until skin was healed.
2.1.2 Control Arm

Aqueous cream was applied by the patient twice a day to treat the control skin areas. If moist desquamation developed in the control areas, these were treated with standard dressings used in the different departments. At the Regional Cancer Treatment Services, any moist desquamation was covered with Systagenix Adaptic Non-Adhering Dressings and held in place with Propax sterile pads. If the patients were suspected to have developed an infection or were observed to have poor wound healing, they were prescribed Flamazine cream with 1.0% Silver Sulfadiazine at the discretion of their referring radiation oncologist.
2.2 **Measurement**

2.2.1 **Skin assessment**

Skin assessments were done 3x a week from the onset of erythema (usually the third week into RT treatment) until completion of treatment using the validated modified Radiation-Induced Skin Reaction Assessment Scale (RISRAS) which was discussed in section 1.5.2. Moist desquamation was recorded as part of the RISRAS assessment. The RISRAS scoring tool also allowed to quantify the development of moist desquamation as the scores are based on the percentage of skin affected by moist desquamation. A score of 1 denotes that the skin affected by moist desquamation covers less than 25% of the study area whereas a score of 6 denotes that the skin affected by moist desquamation covers more than 75% of the study area.

Since the primary aim of the trial was to determine the effects of Mepilex Lite dressings on moist desquamation, the onset of moist desquamation in the study area was additionally recorded along with the date it occurred and its location (i.e. intervention and/or control patch) for each patient. Following treatment, RISRAS skin assessments were done once weekly until skin reactions were resolved. Time to healing was defined as the time it took for complete re-epithelisation. In the case of moist desquamation, this meant the appearance of new pink skin covering the entire area (figure 2.3).

If patients had not experienced moist desquamation whilst on treatment, they were educated on the appearance of moist desquamation. They were instructed to call the research assistant (the author) if moist desquamation occurred between scheduled follow-up skin assessment appointments.
2.2.2 Quality Assurance

Ray Noble-Adams validated the RISRAS scoring system and determined the inter-rater reliability by getting observers to use this tool to assess four photographs and for each photograph, assess four different aspects of radiation-induced skin reactions [57]. They reported reliability coefficients of 0.72, 0.75, 0.69 and 0.64 recognizing that for a newly developed tool, the results for reliability and validity were satisfactory.

To minimise inter-scorer variability in this study, a pre-trial workshop was attended by two radiation therapists from each centre (the research assistant and a backup person) to ensure that the scoring of RISRAS was as consistent as possible. The workshop was facilitated by the Primary Investigator, Dr Patries Herst and Katie Diggelmann, who did all the patient scoring in the previous Mepilex Lite trial [24]. At the workshop, a power point presentation of thirty photographs of acute radiation-induced skin reactions were evaluated using the Modified RISRAS scores and for each photograph the group aimed to reach consensus.
2.2.3 Dose assessment

Dose comparisons were made between the average doses received by the skin in the two arms of the trial. Thermo luminescent dosimeters (TLDs) in Dunedin and film in Auckland Radiation Oncology measured the actual dose delivered to the each skin patch. No direct measurements were done in Wellington or in Palmerston North due to resource constraints in the Medical Physics Departments. In these departments, estimates of skin dose were made using the point dose function on the treatment planning system (XiO Release 4.62.00, CMS Software Elekta Group). The point dose was assessed at five locations in each of the study patches and the average skin dose was calculated for each patch. The aim was to gain an estimate of the relative skin dose in each patch, due to the difficulties in measuring dose in the build-up region. The process was done as follows:

STEP 1: Refer to Figure 2.4

![Diagram showing a template taken on a thin flexible transparent film of the treatment tattoos and the study area together with the scar](image)

Figure 2.4 Diagram showing a template taken on a thin flexible transparent film of the treatment tattoos and the study area together with the scar

STEP 2: Dose was measured at five points in each study patch (i.e. the intervention & the control). Each point was marked on the transparent template 2cm diagonally from the field edge (figure 2.5). The average dose at the markers was used to estimate the dose in each patch.
STEP 3: Measurements were taken to calculate the translational shifts from each reference (ref) tattoo to each marker both in the control and in the intervention patch. Figure 2.6 shows this calculation done for three markers as an example: Usually the ref tattoo closest to the marker was used as this was more accurate.
STEP 4a: In this step, the three setup tattoos were located on the patient’s plan so that translational shifts calculated in step 3 could be applied from each tattoo. To do this, the patient’s plan was accessed on the XiO Planning system where the transverse slice -64.90cm was used to locate the right lateral and the anterior reference tattoos (see figure 2.7).

Figure 2.7 Diagram showing the location of the 3 ref tattoos on transverse Ct slice of -64.9cm

STEP 4b: The patient’s plan data was used to locate the CT Mark coordinates. In this example, the isocentre is on transverse slice -49.70 cm. Using the template, the 3 setup ref tattoos have now been located on the patient’s plan (figure 2.8).
Figure 2.8 Diagram showing the location of the CT Mark tattoo on transverse CT slice of -49.7cm

Figure 2.9 Diagram showing a shift of 4cm inferior from -49.7 to -53.7 and a 1.0cm left shift to localise marker M1 on the skin surface
STEP 5: All the translational shifts calculated in step 3 were applied from each tattoo to locate where each dose point marker would fall. For example, to calculate the distance between CT Mark and control M1 = 4cm INF and 1cm Left. From CT Mark transverse of -49.7cm a 4cm inferior shift was applied which meant that M1 control was situated on transverse slice -53.70cm. On the -53.70cm slice, a ruler was used to measure 1cm left on the scales (which was running through the CT Mark tattoo on the CT mark slice). The dose point M1 Control was located (see figure 2.9). An interest point was placed on the skin at this point which displayed the dose this point was receiving. This process was repeated for each marker.

2.2.4 Initial Skin Assessment
An Initial Skin Assessment Form (Appendix C) was completed for each patient in the trial during their first week of radiation treatment. The initial skin assessment comprised of a summary of each patient’s personal, genetic, and cancer construct together with a summary of the patient’s radiation therapy treatment and any other adjuvant therapy the patient may be on. The form was completed using multiple sources including discussions with the patient, clinical notes accessed using Mosaiq [Mosaiq version 2.00X3 Oncology Management Systems, Inc] and the patient’s green card as well as consultations with each patient’s radiation oncologist. The details included in the initial skin assessment were designed to summarise several related factors that may influence the likelihood of developing a severe radiation-induced skin reactions as discussed in section 1.4.

2.2.5 Exit Questionnaires
Upon completion of the trial, each patient was given the opportunity to comment on different aspects of participating in the trial. This was done using an exit questionnaire completed by each patient (Appendix E).
2.3 Trial Timeline

The Planning CT scan schedule in Mosaiq was used to identify post-mastectomy women requiring radiation therapy to their chest wall. After reading the patient’s clinical notes, their eligibility for the trial was considered. An alert was added to each eligible patient’s CT schedule to remind the Planning CT staff to call the research assistant (the author) to give the patient their post CT information. Every patient in Palmerston North receives a brochure regarding the expected side-effects from their radiation therapy treatment. While this is generally done by planning CT staff, for patients eligible for the trial, the research assistant did this post CT conversation with the patient. This allowed the research assistant to firstly present the patient with the Regional Cancer Treatment Services “Radiation Therapy to the chest wall & General skin care Guidelines” brochure that details the expected skin reaction and then verbally explain the purpose of the Mepilex Lite dressing trial. The patients also received a hard copy of the “Participant information sheet” (Appendix A) that they took home to read.

The research assistant met with the patient on the first day of their treatment to answer any questions the patients had and then obtain informed consent by means on completing the “Informed Consent” form (Appendix B). The RO also signed the consent form indicating that they are aware their patient is enrolled in the Mepilex Lite clinical trial. A “Randomisation coversheet” (Appendix D) was then completed by the research assistant (the author) and faxed to the Principal Investigator in Wellington. The initial skin assessment form was also completed in the first week of treatment.

The treatment radiation therapists alerted the research radiation therapist at the first sign of erythema. Skin patch with erythema was divided into two equal halves and randomised to intervention and control as per the patient’s randomisation sheet. Aqueous cream was obtained from the ROs and Mepilex Lite dressings were supplied by the research radiation therapist. RISRAS assessments were done from the onset of
erythema 3 times a week. A skin template was taken with the patient aligned in the
treatment position to perform dose estimations on XiO planning system. At the
completion of treatment, patients were assessed once a week for up to six weeks or until
the skin reactions resolved which was when patients were asked to complete the exit
questionnaire. The following flow chart summarised the trial timeline:
Figure 2.10 Outlining Trial Timeline

<table>
<thead>
<tr>
<th>Trial Starts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Booking system scanned for eligible patients weekly <strong>Planning CT Scan</strong></td>
</tr>
<tr>
<td>Participant information sheet given to eligible patients by the research assistant and the trial is discussed. &quot;General skin care Guidelines&quot; pamphlet given to the patient.</td>
</tr>
</tbody>
</table>

**Informed Consent**
Research staff meets patients at first fraction.
Informed consent for trial gained
Patient commences aqueous cream over chest wall

**First Week of Radiation Treatment**
Initial Skin Assessment
Randomisation

**First Sign of Erythema**
Treatment staff inform research assistant & area of erythema divided and template taken
Intervention commences
RISRAS assessments 3 x a week.

**Skin Assessments**
RISRAS 3x a week during radiation treatment
1x a week after radiation treatment for up to 6 weeks or till skin is healed

**Trial End**
Resolution of skin reaction or up to 6 weeks post treatment
Exit questionnaire completed
Skin dose assessments completed
2.4 Data collection and Statistical Analysis

The Mosaiq system was utilised to identify potential participants for the trial. Clinical notes in Mosaiq and hard copy medical records were assessed to complete the initial skin assessment form. Windows Excel 2007 (Microsoft Corporation, Redmond, WA) spread sheets were utilized to record RISRAS scores. Skin dose estimations were done using XiO planning systems. All data were emailed to the central trial centre prior to analysis.

The main variables compared between the two arms of the study were the Mean RISRAS scores and the Peak RISRAS scores. Paired two-tailed t-tests were performed using Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA) to determine the statistical significance of differences between RISRAS scores of Mepilex and control skin patches, with \( p < 0.05 \) considered statistically significant.

Additionally the radiation dose received by the skin surface between Mepilex Lite and control patches was also compared, also using paired two-tailed t-tests.

To determine if there was a correlation between the weight and the separation of the chest wall for this cohort, a coefficient of determination \( (R^2) \) was performed.

Qualitative data from the exit questionnaire were transcribed into Microsoft Excel 2007 sheets. Dichotomous data (Yes/No answers) were tabulated and the incidences recorded as percentages. Answers to open questions were subjected to a thematic content analysis.
2.5 **Funding**

Mölnlycke Health Care LTD (Göteborg, Sweden) supplied the trial with free Mepilex Lite dressings. The salary of the principle investigator (Dr Patries Herst) was paid by the University of Otago. The salary of the trial coordinator (Jayne Bowers) and the radiation therapist research assistant (Prashika Poonam) was paid by a University of Otago Research Grant (UORG). Additional costs such as petrol vouchers distributed to patients to reimburse their weekly travel for follow-up assessments were also funded by the UORG. The fees component of the Bachelor of Radiation Therapy (Honours) was funded by the Palmerston Oncology Radiotherapy Trust and the New Zealand Breast Cancer Foundation.

There were no known conflicts of interest between research staff at the Regional Cancer Treatment Services or the University of Otago and Mölnlycke Health Care LTD.
2.6 Amendments

Initially, patients were instructed to apply aqueous cream on the control patch only. Over time it was observed that because the skin under the Mepilex Lite dressing was not moisturized, it became very dry when compared to the control patch. This dryness was visually noticeable and some patients complained of their skin feeling dry under the Mepilex Lite patch. To combat this problem the following amendment was made to the original trial design:

Amendment 1:
Patients were allowed to apply aqueous cream under the Mepilex Lite dressing until the onset of moist desquamation. Patients were directed to wait for the cream to be fully absorbed prior to applying the dressing. Patients were also encouraged to use aqueous cream as a soap substitute due to its emollient properties.

It was found that if patients had not developed moist desquamation by the third week of follow-up, they did not develop moist desquamation after that. This observation resulted in a second amendment of the trial design:

Amendment 2:
The second amendment specified that patients who did not develop moist desquamation in the study area and scored a ‘0’ on the patient component of RISRAS could stop applying the Mepilex Lite dressing from 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 Participant Recruitment and Flow

A pre-trial workshop was held in February 2011 to ensure that the scoring of RISRAS was consistent and to minimize inter-scorer variability. Following this workshop, the trial was initiated at the Regional Cancer Treatment Services from March 2011 until January 2012.

Over this 11 month period, a total of 71 women were referred to the Regional Cancer Treatment Services for post-mastectomy chest wall irradiation. Of these 71 women, 8 women were ineligible due to systematic disease. The Regional Cancer Treatment Services serves a large geographical area and patients from the Taranaki, Hawkes Bay, Napier and Gisborne region would have to travel for at least three hours to get to the hospital and three hours to return back home. A total of 42 women were from these various regions and were therefore ineligible as they were unable to attend the weekly skin assessments post-treatment.

The remaining 21 were eligible and were approached about the trial following their planning CT scan. They were provided with verbal and written information about the trial and were re-visited at their first radiation treatment to establish whether they would like to participate in the trial. A total of 6 patients declined to participate, the reasons for which was not disclosed by 3 of the patients. The other 3 patients could not commit to the weekly follow-up visits due to prior commitments following treatment. A total of 15 patients signed consent for the trial and were randomised. However, one patient withdrew her consent after randomisation, before any skin assessments were done. Another patient did not have any skin reactions during or until three weeks after treatment and consequently did not have any RISRAS scores to be analysed. Therefore, a total of 13 patients were analysed although one of these patients did not attend any
follow-up skin assessments and therefore only RISRAS scores until the last day of her treatment were available for analysis.

The following consort diagram summarizes the details of the recruitment processes:

Figure 3.1 CONSORT Diagram of participant flow
3.2 **Patient Demographics**

Patient demographic details were gathered from the initial skin assessment of the 13 patients included for analysis and are summarised in a table included as Appendix F. The initial skin assessment comprised of a summary of personal, genetic, and cancer construct together with a summary of radiation therapy treatment and any other adjuvant therapy the patient may be having that may influence skin reactions. While the intra-individual nature of this study circumvents the confounding effects of these factors, this information is important because it may allow us to identify factors that contribute to the severity of skin reactions, such as the use of adjuvant chemotherapy, bolus, skin type or smoking status, previous sun exposure etc.

### 3.2.1 Personal Construct (Genetic and Individual)

**Age**

The participant age within this cohort ranged between 29-74 years, with the median age being 51 years. Within the cohort, the percentage of those aged 50 years and over was 61.5%. This is a lower percentage than the 70% reported by New Zealand’s nationwide breast cancer statistics [4].

**Ethnicity and Skin Type**

Eleven participants identified themselves as New Zealand/European. One participant identified as Maori and one as Philippino. Using the “Fitzpatrick Skin Type Guide” (Appendix C) each patient’s skin phenotype was described. Six (46%) patients had “Type 1&2’ skin which is highly susceptible to sunburn, six (46%) patients had “Type 3&4” skin, which is moderately susceptible to the sun and one (7%) patient had “Type 5” skin which generally develops a dark tan but rarely burns.
Separation and Weight:
Participants’ weight varied between 49 to 108kg, (average 77.5kgs ±17.4kg). Separation was measured using the 50% isodose curve that defined the field edge of the medial and lateral tangents. The measurement was done as a straight-line from where the 50% isodose cuts the surface of the skin medially to where it cuts laterally (shown in figure 3.2). The 50% isodose line was used rather than the Planning Target Volume (PTV – demonstrated in magenta) to measure separation because measuring the separation treated by 50% isodose line indicates the separation of the patient receiving high dose. As the isodose lines treat past the PTV, skin reactions did not occur just within the PTV but also outside the PTV and therefore measuring the PTV separation would not indicate the separation of the patient susceptible to a skin reaction. The separation ranged from 25cm to 39cm with an average of 31.3cm. The weight and separation did not show a statistically significant correlation ($R^2=0.242, \ p=0.21$).

Figure 3.2 CT Scan of patient PLM 07 showing the measurement of separation using a straight line following the 50% Isodose curve
**Diagnosis**

Eight (62%) patients presented with cancer in their right breast and five (38%) with cancer in their left breast. The most common diagnosis was infiltrating ductal carcinoma (IDC) affecting eleven (85%) patients. Of these eleven women, one had multicentric IDC and another had multifocal IDC. The remaining two patients from the cohort were diagnosed with lobular carcinoma. One (7%) patient had multiple lobular carcinoma and another (7%) had multifocal lobular carcinoma. Seven (54%) patients had a grade 2 tumour while the remaining six (46%) patients had a grade 3 tumour. The stage of the cancer varied ranging from stage I to stage IIIB. Eleven (85%) patient were estrogen receptor (ER) positive and of these eleven patients, eight patients were also progesterone receptor (PR) positive. Five (38.5%) patients tested positive for human epidermal growth factor receptor 2 (Her2).

**Nutritional Status and Smoking**

Only three (23%) patients reported to have “excellent” nutritional status while majority (69%) reported to have a “good” nutritional status. One (7%) patient reported to have a “fair” nutritional status. Only one (7%) patient was a current smoker in the cohort with nine reporting to have never smoked and three reported as being ex-smokers.

**Co-existing Diseases**

Six patients in the cohort had high blood pressure, two of which also had type II diabetes and heart disease. One of these two patients also reported to have chronic obstructive pulmonary disease (COPD) and an allergy to plasters but none of the participants had an allergic reaction to Mepilex Lite Dressings. One patient also reported to have anaemia.
3.2.2 Therapy Construct

Surgery
All patients (100%) had mastectomy as their primary treatment as well as an axillary lymph node dissection.

Radiation therapy
All the patients were treated with photons and majority received treatment with both 6 and 15 megavoltage (MV) photon beams while two received 15MV alone and one received just 6MV photons. The two most common radiation therapist prescriptions for chest wall treatment in Palmerston North are 5000cGy in 25# and 4005cGy in 15#. In this cohort, ten (76.9%) patients received the fractionation regime of 5000cGy in 25# while the remaining 23.1% received 4005cGy in 15#. All the patients received treatment with tangential beam arrangement with added segmented fields. None of the patients received boost treatment to their chest wall. Twelve (92%) patients had an additional bolus on their chest wall during treatment nine of which were 0.3cm bolus and three were 0.5cm bolus. All patients (100%) received treatment to their axilla and nine (69%) patients received radiation treatment to their supraclavicular nodes.

Chemotherapy
Eleven (84.6%) participants received chemotherapy, eight of which were administered concurrently with RT treatment. Two women started their chemotherapy prior and carried on concurrently with their RT treatment. One woman received and finished chemotherapy prior to RT. All eleven women received fluorouracil also known as 5FU, epirubicin and cyclophosphamide (FEC) chemotherapy drugs. In addition to the FEC, six women received Paclitaxel chemotherapy drug and one patient received Anthracycline. All eleven patients who tested positive for estrogen receptors received hormone therapy treatment regardless of their progesterone receptor status. Nine of these patients received Tamoxifen and the other two patients were prescribed Arimidex. Four out of the five participants who tested positive for HER2 received herceptin.
3.3 **Dose Distribution**

The mean percentage of the prescribed dose on the surface skin under the control and Mepilex Lite dressing patches was estimated to be very similar: 91.70% (SD=8.54%) and 91.83% (SD=9.19%) respectively (Figure 3.3) The difference between the mean skin surface dose was not statistically significant (p=0.9719) demonstrating that any differences in acute skin reactions between control and Mepilex Lite dressing patches is not due to differences in dose.

![Figure 3.3 Estimated Average percentage of prescribed dose to skin patches covered in Mepilex (green bar) and skin patches treated with aqueous control cream (grey bar)]
3.4 RISRAS Scores

The researcher and patient RISRAS scores were added up to establish the combined RISRAS score over the entire time of the trial for both the Mepilex and control patches for each participant (see figure 3.4). The researcher component of the modified RISRAS was completed by the research assistant (the author) and was based on the visual changes observed from the onset of erythema through to moist desquamation. The patient component of the scale was filled in by the patient and scored their skin reaction symptoms. Overall, for majority of the participants the acute skin reactions were less severe in skin covered by the Mepilex Lite dressings.

Figure 3.4 shows that eleven (84.6%) participants had the highest score under the control patch and only one patient (PLM04) had her highest score in the Mepilex Lite dressing patch. It is important to note that for this patient (PLM04) the Mepilex skin patch was located in the axilla but the control was located on the chest wall. The line graphs also illustrate the timing of when the worst skin reactions occurred. For all twelve (92.3%) participants who had follow up appointments, this was after radiation therapy treatment had been completed. Nine patients had their worst skin reaction 1-2 week after treatment, one patient at week 3 and one patient at week 4 post-treatment.
Figure 3.4 Combined RISRAS scores of Mepilex and Control patches for each of the trial participants over time.
3.4.1 Mean RISRAS Scores

The mean RISRAS scores for Mepilex and control patches were calculated for the patient component, the researcher component and the combined scores. In order to compare the results of this trial with a previous trial by our group [24] which reported erythema scores, the average erythema scores for this cohort were also calculated (Table 3.1). A paired samples t-test (2-tailed) was used to determine the statistical significance of the differences in the means.

Table 3.1 Mean Modified RISRAS Scores

<table>
<thead>
<tr>
<th></th>
<th>Mean RISRAS</th>
<th>SD</th>
<th>SEM</th>
<th>Mean Difference</th>
<th>95% CI</th>
<th>p-value</th>
<th>% Increase in Control</th>
<th>% Decrease in Mepilex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined RISRAS</td>
<td>Mepilex</td>
<td>1.87</td>
<td>1.09</td>
<td>0.30</td>
<td>-1.13</td>
<td>-1.75, -0.51</td>
<td>0.002*</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>3.00</td>
<td>1.47</td>
<td>0.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Researcher RISRAS</td>
<td>Mepilex</td>
<td>1.66</td>
<td>0.78</td>
<td>0.22</td>
<td>-0.39</td>
<td>-0.71, -0.14</td>
<td>0.008*</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>2.05</td>
<td>0.73</td>
<td>0.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient RISRAS</td>
<td>Mepilex</td>
<td>0.22</td>
<td>0.39</td>
<td>0.11</td>
<td>-0.73</td>
<td>-1.17, -0.28</td>
<td>0.004*</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>0.95</td>
<td>0.81</td>
<td>0.23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema RISRAS</td>
<td>Mepilex</td>
<td>1.35</td>
<td>0.47</td>
<td>0.13</td>
<td>-0.24</td>
<td>-0.46, 0.02</td>
<td>0.037*</td>
<td>85</td>
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<tr>
<td></td>
<td>Control</td>
<td>1.59</td>
<td>0.40</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant

Mepilex Lite dressings significantly reduced the combined RISRAS scores for acute skin reactions by 38% (p=0.002). The differences in the mean researcher and patient scores both showed a significant reduction in acute skin reactions in favour of the Mepilex arm. However, the mean combined RISRAS scores were heavily influenced by the patient component of the RISRAS, with a 77% (p=0.008) reduction in mean patient RISRAS scores for the Mepilex Lite dressing patches. The dressings also significantly reduced the average erythema score by 15% (p=0.037).
The effect of Mepilex Lite on the average combined, researcher and patient RISRAS scores as well as the erythema RISRAS scores are illustrated in Figure 3.5.

Figure 3.5 Comparison of mean RISRAS scores of Mepilex Lite patches (green bars) and Control patches (grey bars)
3.4.2 Peak RISRAS Scores

While the mean RISRAS scores offers the opportunity to observe the overall magnitude of skin reactions in the two arms of the study, due to the way it is calculated, the severity of the skin reactions are not revealed as the extreme RISRAS scores are not considered on their own. The manifestation of the maximum severity of the skin reactions is important to consider as this is what the patient would experience. Peak RISRAS scores were defined as the maximum RISRAS score at any time of the patient’s progression through the trial. RISRAS scores were again divided into four constituents; combined RISRAS, researcher RISRAS, participant RISRAS, and erythema RISRAS scores for the two arms of the study. For each patient, the maximum scores for each of the constituents in the two arms were recorded and the mean peak score was calculated followed by the difference in the mean between the Mepilex and the control arm. Using the Paired Samples t-test (2-tailed), the statistical significance of the difference in the means was determined and is presented in table 3.2.

<table>
<thead>
<tr>
<th>Table 3.2 Peak Modified RISRAS Scores</th>
<th>Mean Peak RISRAS</th>
<th>SD</th>
<th>SEM</th>
<th>Mean Difference</th>
<th>95% CI</th>
<th>pvalue*</th>
<th>% Increase in Control</th>
<th>% Decrease in Mepilex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined RISRAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepilex</td>
<td>4.23</td>
<td>3.64</td>
<td>1.01</td>
<td>-3.19</td>
<td>-5.23, -1.15</td>
<td>0.005*</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>Control</td>
<td>7.42</td>
<td>4.45</td>
<td>1.24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Researcher RISRAS</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepilex</td>
<td>3.58</td>
<td>2.44</td>
<td>0.68</td>
<td>-0.88</td>
<td>-1.65, -0.12</td>
<td>0.026*</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>Control</td>
<td>4.46</td>
<td>2.25</td>
<td>0.62</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient RISRAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepilex</td>
<td>0.77</td>
<td>1.36</td>
<td>0.38</td>
<td>-2.23</td>
<td>-3.67, -0.79</td>
<td>0.006*</td>
<td>26</td>
<td>74</td>
</tr>
<tr>
<td>Control</td>
<td>3.00</td>
<td>2.45</td>
<td>0.68</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema RISRAS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mepilex</td>
<td>2.23</td>
<td>1.01</td>
<td>0.28</td>
<td>-0.54</td>
<td>-0.94, -0.14</td>
<td>0.012*</td>
<td>81</td>
<td>19</td>
</tr>
<tr>
<td>Control</td>
<td>2.77</td>
<td>0.83</td>
<td>0.23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Statistically Significant

The peak RISRAS scores were similar to those of the average RISRAS scores in that both were in favour of Mepilex Lite dressings. Mepilex Lite dressings significantly reduced
the combined peak RISRAS scores by 43% (p=0.005). Peak patient RISRAS scores showed a large 74% reduction and this was statistically significant (p=0.006). The difference in the peak researcher score between the Mepilex and control also showed a significant reduction in severity of the skin reactions in favour of the Mepilex arm (p=0.026) showing a 20% of reduction peak RISRAS scores. Overall, the severity of erythema in the control arm was 81% higher in the control patch when compared with the Mepilex skin patch (p=0.012). The effect of Mepilex Lite on the peak combined, researcher and patient RISRAS scores as well as the erythema RISRAS scores are illustrated in Figure 3.6.

Figure 3.6 Comparison of Peak RISRAS Scores of Mepilex Lite patches (green bars) and Control patches (grey bars)
3.5  **Moist Desquamation**

Any moist desquamation in the control patch was treated as per standard department protocol which entailed the use of Systagenix Adaptic Non-Adhering Dressings held in place with Propax sterile pads. If case of an infection or poor wound healing, Flamazine cream with 1.0% Silver Sulfadiazine was prescribed at the discretion of the referring radiation oncologist. However, because Regional Cancer Treatment Services treats patients from such a large geographical area, many of the out of town patients would receive a referral for a district nurse to care for their moist desquamation post-treatment. Every patient on the trial who had moist desquamation on the chest wall excluding the intervention patch was given a referral for a district nurse together with information for the district nurse regarding the patient’s trial enrolment details. This was done to ensure that district nurses did not dress the intervention patch with standard care dressings. At the completion of the trial, the patients could present with any of the following four possible scenarios:

1. No moist desquamation in the control or the intervention patch
2. Moist desquamation in the control patch only
3. Moist desquamation in the intervention patch
4. Moist desquamation in both the study areas

Figure 3.4 explains how each of the above scenarios would have been approached. In the current trial, all patients presented with no moist desquamation in either of the study patches on the last day of treatment.
Figure 3.7 Outlining the four possible pathways for the presentation of moist desquamation
3.5.1 Incidence of Moist desquamation

All the participants in the cohort experienced moist desquamation in different locations but only 62% of these were in the study area. The control patch had eight incidences of moist desquamation (62%) whereas the Mepilex Lite dressings had five incidences (38%) as outlined in table 3.3.

<table>
<thead>
<tr>
<th>Participants</th>
<th>Incidence of MD under Mepilex</th>
<th>Incidence of MD in Control</th>
<th>Incidence of MD but outside study area</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLM01</td>
<td>Y</td>
<td>Y</td>
<td>Y (Axilla+ chest wall)</td>
</tr>
<tr>
<td>PLM04</td>
<td>Y</td>
<td>Y</td>
<td>Y (Axilla)</td>
</tr>
<tr>
<td>PLM05</td>
<td>N</td>
<td>N</td>
<td>Y (Axilla)</td>
</tr>
<tr>
<td>PLM06</td>
<td>Y</td>
<td>Y</td>
<td>Y (Axilla+ chest wall)</td>
</tr>
<tr>
<td>PLM07</td>
<td>N</td>
<td>N</td>
<td>Y (Axilla)</td>
</tr>
<tr>
<td>PLM08</td>
<td>Y</td>
<td>Y</td>
<td>Y (Axilla+ chest wall)</td>
</tr>
<tr>
<td>PLM09</td>
<td>N</td>
<td>Y</td>
<td>Y (Axilla)</td>
</tr>
<tr>
<td>PLM10</td>
<td>N</td>
<td>N</td>
<td>Y (Axilla)</td>
</tr>
<tr>
<td>PLM11</td>
<td>N</td>
<td>N</td>
<td>Y (Axilla)</td>
</tr>
<tr>
<td>PLM12</td>
<td>N</td>
<td>Y</td>
<td>Y (Axilla)</td>
</tr>
<tr>
<td>PLM13</td>
<td>Y</td>
<td>Y</td>
<td>Y (Axilla+ chest wall)</td>
</tr>
<tr>
<td>PLM14</td>
<td>N</td>
<td>Y</td>
<td>Y (Axilla)</td>
</tr>
<tr>
<td>PLM15</td>
<td>N</td>
<td>N</td>
<td>Y (Axilla)</td>
</tr>
</tbody>
</table>

| Percentage   | 38%                            | 62%                        | 100%                                  |

All five patients who developed moist desquamation in the Mepilex study area also developed moist desquamation under the control patch. PLM04 had her Mepilex Lite dressing patch located in the axilla while the control patch was located on the lateral chest wall. Three patients developed moist desquamation under the control patch but not under the Mepilex Lite dressing patch. All patients developed moist desquamation under the axilla at some stage during the trial. This demonstrates that in these patients, it is the axilla that suffers most from severe skin reactions. This is likely due to the fact that the skin in the axilla is subject to friction with the skin of the upper arm as well as from clothing. In addition, moisture from perspiration is likely to build up in this area, exposing the radiation-damaged skin to additional mechanical and chemical stress.
The Mepilex dressings have been shown to minimize friction between the radiation-damaged skin and other parts of the body or clothing. However, it was difficult to fit the dressings in the axilla without it rolling up or slipping off. This may have contributed to PLM04 developing MD in her axilla even though the axilla was covered in Mepilex.

Overall, while a difference in the incidence of moist desquamation was noted between the Mepilex and the control arm, due to the small sample size (n=13) and the low incidence of moist desquamation in the study area, it cannot be determined whether this difference is statistically significant.
3.5.2 Mean and Peak RISRAS scores for Moist Desquamation

The RISRAS scores for moist desquamation are based on the percentage of surface area of skin affected. Comparing the mean and peak moist desquamation scores demonstrates the difference between Mepilex and control patches with respect to the mean and peak percentage of skin surface affected. Using the Paired Samples t-test (2-tailed), the statistical significance of the difference in the means between Mepilex and control patches was determined and is presented in table 3.4.

Table 3.4 Comparison of the Mean and Peak RISRAS score in the Mepilex and Control patches

<table>
<thead>
<tr>
<th></th>
<th>Mean MD RISRAS</th>
<th>Peak MD RISRAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mepilex</td>
<td>Control</td>
</tr>
<tr>
<td>Mean RISRAS</td>
<td>0.18</td>
<td>0.29</td>
</tr>
<tr>
<td>SD</td>
<td>0.29</td>
<td>0.40</td>
</tr>
<tr>
<td>SEM</td>
<td>0.08</td>
<td>0.11</td>
</tr>
<tr>
<td>Mean Difference</td>
<td>-0.11</td>
<td></td>
</tr>
<tr>
<td>pvalue</td>
<td>0.04*</td>
<td></td>
</tr>
<tr>
<td>% Increase in Control</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>% Decrease in Mepilex</td>
<td>38</td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant

The percentage of skin surface experiencing moist desquamation was 38% lower under the Mepilex dressings compared with the control patch ($p=0.04$). Similarly, on average, the largest percentage of skin surface affected under the Mepilex Lite dressing was 46% lower than the control patch ($p=0.02$). The average surface area of the chest wall included in the study patch was on average 80cm$^2$ and often only covered less than a third of the chest wall. Patients find moist desquamation difficult to manage and even a small skin patch with moist desquamation will have an impact on the patient’s quality of life. A smaller patch of moist desquamation is easier to dress and manage, less painful and heals faster [44].
3.5.3 Time to Onset and Healing

Time to onset of moist desquamation was analysed (in days) from the first day of treatment to the first day the patient presented with moist desquamation. Time to healing was determined as the number of days from the day moist desquamation was first presented to the day of the post treatment visit when the skin had reached complete re-epithelisation (new pink skin) over the area of moist desquamation.

Table 3.5 Time to Onset and healing of MD in the Mepilex and Control patch for individual patients

<table>
<thead>
<tr>
<th></th>
<th>Time to MD Mepilex (Days)</th>
<th>Time to MD Control (Days)</th>
<th>Time to Healing Mepilex (Days)</th>
<th>Time to Healing Control (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLM01</td>
<td>50</td>
<td>50</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>PLM04</td>
<td>44</td>
<td>65</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>PLM06</td>
<td>43</td>
<td>42</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td>PLM08</td>
<td>49</td>
<td>49</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>PLM09</td>
<td>-</td>
<td>35</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>PLM12</td>
<td>-</td>
<td>49</td>
<td>-</td>
<td>6</td>
</tr>
<tr>
<td>PLM13</td>
<td>37</td>
<td>37</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>PLM14</td>
<td>-</td>
<td>39</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td><strong>Average (Days)</strong></td>
<td><strong>44.6</strong></td>
<td><strong>45.8</strong></td>
<td><strong>14.6</strong></td>
<td><strong>13.5</strong></td>
</tr>
</tbody>
</table>

MD= Moist Desquamation

The onset of moist desquamation occurred after completion of treatment in all patients. The onset and healing of moist desquamation was recorded at post-treatment weekly visits unless moist desquamation or healing occurred in between weekly visits, in which case patients rang the research assistant (the author) to schedule a visit for a skin assessment sooner. There were no differences between the two arms with respect to the time to developing moist desquamation and the time to healing.
3.6  Exit Questionnaires

Patients who did not develop moist desquamation by their third week follow-up skin assessment did not continue follow up visits and were given an exit questionnaire at this visit. Patient who developed moist desquamation were given the exit questionnaire when their moist desquamation had resolved. A total of 12 patients (92.3%) were given exit questionnaires and all were returned for analysis. Since PLM 15 did not return for any further follow-up visits, she did not receive an exit questionnaire. Therefore, twelve questionnaires were analysed. The questionnaire gave the participants an opportunity to reflect on their experience in taking part in this trial and in using the dressings.

3.6.1  Trial Experience

All patients maintained that participation in the trial had been a positive experience. Women reported feeling interested and content with taking part in study/research that is likely to improve management of skin reactions in the future.

“Nice to be made aware, and be involved in a continuing improvement in the way the skin damage is managed” PLM04

“Glad to be part of it, Knowing that research is being done” PLM06

“Interested in research process & happy to contribute to new learning that may prove useful to others” PLM12

Participants also commented on the added benefit of having a qualified staff continuously monitoring their skin each week after treatment. Responses highlighted that patients were uncertain about what to expect with regards to skin reactions post-treatment and felt much safer with a continued interaction with a medical professional.
“I like the follow up once the radiation treatment was finished. I felt secure that someone was continuing to check my wound” PLM10

“4 weeks of ‘check-in’ after end of treatment felt like a “safety net’ as radiation continued to work in my body & I was not sure what to expect exactly & how I would manage if skin had broken badly” PLM12

One woman appreciated the availability of the Mepilex Lite dressing from the start of erythema as opposed to using the cream.

“Through this trial I would rather have the dressing not the cream” PLM01

Another patient commented on how easy it was to use the Mepilex Lite dressings which made being in the trial a positive experience.

“I found it easy to use and very comfortable” PLM13

The friendly and professional attribute of the research assistant (the author) was also mentioned as making the trial a positive experience as well as their expert knowledge on skin reactions.

“[Name] clear about process. Informative about other sources- i.e. I had questions that arose beyond the treatment period that she was able to answer on the spot” PLM12

“Staff were professional and friendly” PLM14

3.6.2 Effectiveness of Mepilex Lite dressings

Participants were asked to give their opinion of whether or not they thought that the Mepilex Lite dressings were superior to the cream in managing their skin reactions. Eleven women responded with a yes giving various reasons for their answer while
two women were unsure. The majority of the women commented on the visible differences that they saw with the two arms of the treatment.

“The area covered by the dressing took longer to become ‘flaky’. A small part did not become flaky at all’ PLM12

“Yes the skin under the Mepilex was less red” PLM14

“The dressing site …certainly hasn’t peeled as much…” PLM09

Majority of the patient made more subjective symptomatic remarks with regards to how the skin felt and their observation of how soon it healed.

“Yes, the dressings are far better. I had very little itchiness and soreness at all” PLM01

“The dressing site certainly healed faster…+ wasn’t itchy…” PLM09

“Yes it was less sore…less irritated under dressing” PLM11

“The area seem to heal quicker” PLM13

Participants commented on the protective attribute of the dressing that they felt their skin lacked with the use of the cream. PLM04 reported that she wasn’t sure if the dressing were superior to the cream in managing the skin reactions but did note the protective characteristic of the dressing that comes from covering the skin.

“Not sure. Definitely preferred having the area covered/protected thou [sic]” PLM04

“Although I only had a slight reaction of the radiation, I found the dressing better under clothing as it protected by skin from rubbing + itching” PLM07
PLM06 felt she was not sure about whether or not she thought the dressings were better but her response highlighted that she was weary of her bad moist desquamation experienced outside the study patch.

“Not really sure, but my under arm reacted badly” PLM06

3.6.3 Advantages of Mepilex Lite Dressings

In addition to the large quantity of comments about how Mepilex Lite dressings helps reduce and manage skin reactions, the majority of the patients identified that the dressings was “easy” to use and manage as well as being “comfortable”. This is an important characteristic of any dressing used to manage radiation-induced skin reaction especially moist desquamation. Moist desquamation is usually seen up to 2 weeks post treatment and can take up to 4-6 weeks post-radiation treatment to heal [37]. As patients do not get the same daily medical attention post treatment as they do during their radiation therapy treatments, it is important that they have a dressing that is easy to use and comfortable.

“The dressing were easy to apply, once on they were comfortable, hardly knew they were there. PLM01

“Easy, comfortable, simple, non-messy” PLM05

“Easy to use + comfortable, molded to the body” PLM09

“Less messy than the cream. Easy to apply to skin that had not had cream applied” PLM12

3.6.4 Disadvantages of Mepilex Lite dressings

Half the patients (50%) reported that Mepilex Lite dressings had no disadvantages. Four patients (33%) identified the lack of adherence of the dressing to skin during activities or at night. Patients who were enrolled in the trial over summer also commented on how the dressing was less adherent in warmer temperatures.
“...but they didn’t stick very well” PLM01

“at times the dressings would come off... as the weather got warmer & I started to sweat, it just fell off when doing day to day things” PLM09

“They didn’t stick very well to the skin.” PLM10

“Dressing fell off during exercise when I became very sweaty” PLM12

The size of the Mepilex Lite dressings provided to the patient depended on the size of the skin that showed first sign of erythema which was then divided into half. However, two patients commented that one of the disadvantages of the Mepilex Lite dressing for them was the small size of Mepilex Lite dressing patch. They indicated that larger sizes would have been more beneficial.

“Different sizes might be beneficial” PLM04

“Bigger dressings would have been better as it was hard to manage with another different type of dressing under my arm” PLM11

One patient also reported forgetting to put on the Mepilex Lite dressing.

“No disadvantages except for remembering to put it on”

Overall, 100% of the patients stated that based on their experience of participating in this clinical trial, they would participate in other clinical trials when appropriate.
4 DISCUSSION

The overarching aim of this clinical trial was to investigate whether Mepilex Lite dressings were superior to the control aqueous cream in reducing the incidence and extent of radiation-induced skin reactions in breast cancer patients post-mastectomy. This section discusses aspects of the trial methodology and study results that may have impacted on the results in some way, either strengthening or weakening the conclusions. This thesis describes and analyses the results of 13 patients recruited at the Regional Cancer Treatment Services who were a subset of the large 80 patient multicentre trial. Results from the full multicentre trial have been accepted for publication on 27 September 2012 in the Journal of Cancer Science and Therapy.

4.1 Study Methodology

4.1.1 Patient inclusion and exclusion criteria
The post-mastectomy skin surface is an excellent model to test skin care protocols as it provides a relatively uniform surface and receives a relatively uniform radiation dose when compared to other sites where radiation-induced skin reactions are common [26]. Women with previous RT to the chest wall or metastatic disease, breast reconstruction surgery, impaired mobility, and Karnofsky performance status scores of less than 70 were excluded. Women who were unable to come back to the department for additional skin assessments once a week post treatment until the final check-up at 6 weeks were also excluded.

A total of 13 patients from Regional Cancer Treatment Services fitted the inclusion and exclusion criteria of the trial and were included in the study.

4.1.2 Intra-patient controls
One of the strengths of this trial was that the patients acted as their own control thus minimizing the confounding effects of patient-related and treatment-related factors.
4.1.3 Randomisation

Randomisation using computer generated numbers was also a strength of this trial as it minimized any small differences in dose received by the control and Mepilex Lite skin patches (as was figure 3.3).

4.1.4 Aqueous cream

Aqueous cream was a good control for this trial as it is standard care at Regional Cancer Treatment Services. Aqueous cream is used for radiation-induced skin reactions in 70% of radiation therapy departments in New Zealand and Australia. This is despite the findings of a large randomised controlled clinical trial (RCT) (n=357) which showed that aqueous cream does not prevent nor decrease the severity of skin reactions [70].

The trial methodology was modified early on in the trial because the skin under the Mepilex Lite dressings became rather dry. Patients were advised to apply aqueous cream under the Mepilex Lite dressing patch once a day and wait for the cream to be fully absorbed prior to applying the dressing. Patients were also encouraged to use aqueous cream as a soap substitute because of its emollient properties. In addition to the aqueous cream, seven patients were also treated with 1% hydrocortisone to help soothe the itching associated with dry desquamation.

4.1.5 Measurements

The Modified RISRAS skin assessment tool was used to score radiation-induced skin reaction (refer to section 1.5.2). The Modified RISRAS categorises skin reactions into erythema, dry and moist desquamation and necrosis instead of clustering skin reactions together, as is done with other skin reaction assessment scales such as RTOG [53]. This allows for a greater discrimination between small differences in skin reaction severity. This scale also recognises that the severity of the skin reaction within a treatment area is not uniform by basing the scores on percentage of surface area of skin affected skin.
The total RISRAS score for each arm of the study were calculated as a product of the researcher RISRAS scores and the participant RISRAS scores. Erythema scores from the researcher component were analysed independently for a direct comparison with the results of the previous Mepilex Lite trial of Diggelmann et al. [24]. Therefore, analyses were performed for the Researcher, Erythema, Participant and Combined RISRAS scores. Mean and peak scores were calculated for both Mepilex Lite and control skin patches.
4.2 Interpretation of results

4.2.1 Modified RISRAS Analysis

Researcher RISRAS Scores (including Erythema RISRAS Scores)

The mean erythema scores revealed that Mepilex Lite dressings significantly decreased the extent of erythema by 15% (p=0.037) and the severity of erythema by 19% (p=0.012) compared with control patches. These results were similar to those of the pilot trial by Diggelmann et al. [24] which used the Modified RISRAS to evaluate the effect of Mepilex Lite dressings on erythema with a trial endpoint of dry desquamation. The authors reported that Mepilex Lite dressings decreased the extent of erythema by 32% with a strong statistical significance of \( p<0.001 \).

The statistical significance of Diggelmann’s study surpasses that of this clinical trial. This is most likely due to the larger sample size of the pilot study (n=24) compared to this study (n=13). Analysis of all 80 patients in the current multi-centre study showed a statistical significance of \( p<0.001 \) (accepted for publication on 27 September 2012 in the Journal of Cancer Science and Therapy.).

This is the first study that has evaluated the effect of Mepilex Lite dressings on all aspects of radiation-induced acute skin reactions and not just erythema. Overall, the researcher RISRAS scores showed that Mepilex Lite dressings significantly reduced the visual extent of radiation-induced skin reactions by 19% (p=0.008) and the peak researcher RISRAS by 20% reduction (p=0.026). These results are consistent with the erythema scores of the previous pilot trial [24] and support the hypothesis that the dressings provide physical protection against mechanical damage and stop premature loss of skin integrity during the healing process.

Patient RISRAS Scores

Radiation skin reactions can directly affect a patient’s quality of life by causing pain and discomfort, and by limiting daily activities. In view of this, the patient
component of the modified RISRAS scores is clinically relevant as it is a subjective measure of symptoms including pain, tenderness, discomfort, itchiness, and burning sensation in the irradiated area. It also measures to what extent the irradiated skin reactions symptoms have affected the patient’s day-to-day activities. Interestingly the mean patient RISRAS scores demonstrated a much greater decrease in severity and peak skin reactions than the researcher RISRAS scores (by 77%; \( p=0.004 \) and 74%; \( p=0.006 \) respectively).

**Combined RISRAS Scores**

Significant decreases in researcher and patients RISRAS scores in favour of the Mepilex Lite dressings resulted in a substantial decrease in mean combined RISRAS scores (38%, \( p=0.002 \)) and combined peak RISRAS scores (43%, \( p=0.005 \)). It is important to note that the decrease in radiation skin reaction in both the mean and the peak combined RISRAS score in the Mepilex Lite patches is strongly influenced by the patient component of the RISRAS for this cohort of patients. Although patient RISRAS scores are highly subjective, they do reflect the patient’s experience of the skin reactions and their effect on daily life. The differences in the researcher and patient mean and peak scores in this study confirm findings of Porock and Kristjanson [48] who reported that the outward presentation of skin reactions does not equate to the way the symptoms are actually experienced by patients. These authors have stated that it is essential that any skin damage caused by radiation therapy is minimised, as far as possible, by ensuring that interventions are based upon best practice and supported by evidence-based guidelines [20]. The current study findings support that Mepilex Lite dressings reduce the visible extent of radiation skin reactions and provide symptomatic relief for the patients.

**4.2.2 Moist Desquamation**

**Incidence of Moist desquamation**

Moist desquamation is perhaps the most clinically significant skin reaction because it is the most painful and difficult to manage radiation-induced skin toxicity [46]. In
spite of this, there is a paucity of evidence to support the use of wound care products for moist desquamation reactions, and understandably remains an area of considerable controversy [63, 110, 111]. Characterised by blistering and peeling of the irradiated skin, severe moist desquamation may result in treatment delays, which may affect the final outcome [112]. In addition, patients experience considerable distress as a result of skin damage due to moist desquamation.

The Regional Cancer Treatment Services does not systematically record the occurrence and severity of skin reactions. This made it difficult to define the “normal baseline” incidence of moist desquamation. In this cohort, incidence of moist desquamation in the control arm was 62% compared with 38% in the Mepilex Lite arm. The incidence of moist desquamation in the control arm was higher than that of Graham and his colleagues [26], who reported a 46% incidence rate in 62 post-mastectomy patients treated with sorbolene cream (which is very similar to aqueous cream).

However, since the locations of the Mepilex Lite and control patches were determined by where the area of the irradiated skin first developed erythema, the entire treatment area was not included in the study. To determine the true incidence of moist desquamation in this cohort, any moist desquamation occurring outside the study area within the tangential treatment fields was systematically recorded. This lead to an unexpected finding; all (100%) patients were found to develop moist desquamation in their axilla.

All patients (n=5) who developed moist desquamation in the Mepilex Lite patch also developed moist desquamation in the control patch and four of these developed moist desquamation in other parts of their chest wall. PLM04 was the only patient who developed moist desquamation in both Mepilex Lite and control patches but nowhere else on the chest wall. She was also the only patient who had part of her study patch under the axilla (Mepilex Lite patch) and part of her study area on the chest wall (control patch).
As all the patients in this cohort developed moist desquamation in the axilla, this implies that the axilla is most likely to develop severe skin reactions. This is not surprising as the skin in the axilla is subject to friction with the skin of the upper arm as well as from clothing. In addition, moisture from perspiration is likely to build up in this area, exposing the radiation-damaged skin to additional mechanical and chemical stress [44]. Mepilex Lite dressings minimize friction between the radiation-damaged skin and other parts of the body or clothing. However, it was difficult to fit the dressings in the axilla without them rolling up or slipping off. This is likely to have contributed to PLM04 developing moist desquamation in the axilla even though the axilla was covered in Mepilex Lite dressings.

The benefits of Mepilex Lite dressings were best observed in the three patients who developed moist desquamation in the control patch but not in the Mepilex Lite dressing patch or any other parts of the chest wall. In these patients, both the patches were located on the chest wall surface, unlike PLM04, who had her Mepilex Lite dressing patch located in the axilla. This meant that neither of the patches was subjected to additional friction or moisture from perspiration and there was no measurable difference in dose received by both skin patches. Only the skin treated with aqueous cream developed moist desquamation whereas the skin underneath Mepilex Lite remained intact. This supports the hypothesis that Mepilex Lite dressings reduce the extent of radiation-induced skin reactions by providing the physical protection needed against this mechanical damage and stopping premature loss of skin integrity during the healing process. In these three patients, the presence of Mepilex Lite dressings has clearly reduced friction by acting as a protective barrier between the irradiated skin and clothes or adjacent tissue.

Incidence of moist desquamation alone does not signify the severity of the skin reaction as experienced by the patient. The Modified RISRAS scores for moist desquamation are based on the percentage of skin surface affected with 0 indicating no area of skin affected, a score of 1.5 referring to less than 25% of the skin affected, 3.0 pertaining to 25-50% of the skin surface and a score of 6 denoted for more than
75% of the skin surface area affected. A comparison of the average and peak moist desquamation RIRAS scores demonstrated the percentage of skin surface experiencing moist desquamation was 38% lower under the Mepilex dressings compared with the control patch \( (p=0.04) \). Similarly, the largest percentage of skin surface affected under the Mepilex Lite dressing was 46% lower than the control patch \( (p=0.02) \).

The clinical relevance of these findings justifies the need for further research. Moist desquamation not only causes great discomfort, it also causes disruption to the daily lives of patients \([44]\). Additionally, research suggests that small areas of moist desquamation tend to heal from the basal layer, whereas large areas of broken epidermis require cells to migrate from the surrounding epidermis hence taking longer to heal \([38]\). Therefore, by reducing the area of skin surface affected, the wound will be easier to dress and manage, may heal quicker and also decrease the extent to which it affects the patient’s ability to perform their day to day activities.

**Time to Onset and Healing**

The secondary objectives of this study were to determine whether Mepilex Lite dressings increased the time to onset of moist desquamation and/or decreased the time to healing when compared to the standard dressings. Results showed that there were no differences between the time to developing moist desquamation or in the time for moist desquamation to heal.

Interestingly, twelve patients had their worst skin reactions subsequent to the completion of their radiation therapy. One patient did not attend any follow up visits so no RISRAS scores were done after the completion of treatment. Nine patients had their worst skin reaction 1-2 week after treatment, one patient at week 3 and one patient at week 4 post-treatment. All of the episodes of moist desquamation were first noted in either the first or second week post-treatment. This is similar to Graham et al. \([26]\) and other previous studies \([40, 44, 66, 71]\) that report that peak skin reactions occurred after treatment completion.
The clinical implications of this delay in the manifestation of severe skin reactions highlight the importance of patient follow up post-treatment. At the Regional Cancer Treatment Services, post-mastectomy patients attend treatment from a wide geographical area and usually only those patients who have experienced moist desquamation while on treatment receive a district nurse referral for skin care management. Nurses sometimes also gauge if the skin may break down depending on the appearance of the skin and provide a district nurse referral. The rest of the patients are given a contact number for the department and encouraged to call if they have any concerns in terms of side effects. In the current cohort, none of the patients had experienced moist desquamation throughout the course of the treatment. Only one (7.7%) patient (PLM15) was given a district nurse referral on her last day of treatment based on her skin appearance, but she did not attend for any further RISRAS scoring post-treatment. The rest of the twelve patients (92.3%) who returned for follow up RISRAS scoring ended up receiving a district nurse referral post-treatment following their visit with the research assistant (the author). A significant percentage of the cohort therefore did not get a district nurse referral at their discharge appointment, nor did they call the department back to discuss the progression of the severity of their skin reaction with a nurse.

The management of moist desquamation is difficult because, unlike other stages of radiation-induced skin reactions, the skin is open and susceptible to infection [62]. Patients need to be educated to be able to identify the presence of moist desquamation and made aware of the importance of optimal wound management. Additionally, a more rigid follow up system needs to be implemented to ensure that all patients readily have access to a health care professional to provide them with expert advice. In a recent study conducted by Cumming and Routsis [113], a suggestion was made to implement a courtesy follow up telephone call from a radiation therapist one to two weeks after treatment. The main concern from the clinical staff at the Regional cancer Treatment Services with this suggestion was the difficulty in providing advice without being able to visually assess the skin reaction.
A solution to this would entail role enrichment whereby a radiation therapist would be employed who would make follow-up visits to each geographical area. Then they would be able to visually assess the skin reactions and provide advice for optimal management. Lack of time and resources are the main hurdles to implementing such a provision in care [113].

4.2.3 Exit Questionnaires

The exit questionnaire gave the participants an opportunity to reflect on their experience and make comments on taking part in this trial and in using the dressings. Twelve patients (92.3%) were given exit questionnaires and all were returned for analysis. Since PLM 15 did not return for any further follow-up visits, she did not receive an exit questionnaire. All patients declared that participation in the trial was a positive experience. Most women felt contented as well as interested in taking part in a study/research that would improve management of skin reactions for other women in the future.

It is well documented that moist desquamation reactions can be extremely difficult to manage [20, 40, 44, 113], hence it was no surprise that participants spoke out strongly in favour of the added benefit of having qualified staff continuously monitoring their skin each week after treatment. It was also apparent from the responses that patients felt uncertain about what to expect with regards to skin reactions post-treatment and felt more secure with continued interaction with a friendly medical professional.

Advantages of Mepilex Lite

Responses relating to the advantages of Mepilex Lite dressings correlated well with the results of the patient RISRAS scores. With the exception of two patients (PLM04 & PLM06), ten women thought that the Mepilex Lite dressings were superior to the cream in managing their skin reactions. Patients commented on the visible difference that they could see on their chest wall between the two patches. The majority of the patients commented on how good the skin felt and how soon it healed. Even PLM04,
who reported that the dressings in the axilla kept rolling up or slipping off, noted the protective characteristics of the dressing.

In 2008, MacBride et al. [44] conducted a case study with the primary aim of evaluating how easy to use and comfortable Mepilex Lite dressings were in the management of radiation-induced skin reactions. Their results suggested that most patients found the dressing comfortable to wear and to remove. These findings were confirmed by Diggelmann and her colleagues [24] who also reported that Mepilex Lite dressings increased patient comfort as well as quality of life. A thematic analysis of the exit questionnaires showed that these reports were consistent with the current study where a large number of women reported that the dressings were “easy” to use and manage as well as being “comfortable”. This is an important characteristic of Mepilex Lite that enables it to be used as a dressing to manage radiation-induced skin reaction, especially moist desquamation. Moist desquamation is usually seen and is at its peak 1-2 weeks after treatment and can take up to 4-6 weeks to heal post-radiation treatment [37]. As patients do not get the same daily medical attention post-treatment as they do during their radiation therapy treatments, it is vital that they have a dressing that is easy to use and comfortable.

MacBride et al. [27] also found that, in many cases, the use of Mepilex Lite dressings had a considerable (and sometimes immediate) impact on activities of daily living including sleeping, wearing clothes, and using a car seat belt. A similar experience was also highlighted by patients in the current cohort who wrote about the advantage of having the skin covered, providing added protection during their daily lives.

Disadvantages of Mepilex Lite

Although 50% of patients reported no disadvantages, some identified the lack of adherence of the small piece of dressing when partaking in activities during the day and sleeping at night. Patients who were enrolled in the trial over summer also commented on how the dressing seemed to adhere poorly in warmer temperatures.
It is possible that the trial amendment relating to the use of aqueous cream underneath the dressings may have compromised the adherence of the dressings. The amendment was put in place to stop the skin underneath the dressings from getting too dry.

Patients indicated that larger dressings would have been more beneficial. Due to the design of the study, the patch of skin being covered with Mepilex Lite dressings was often small, depending on the size of the skin patch that first presented with an erythematous skin reaction. In addition, patients had to manage two different types of dressings/cream on their chest wall throughout their daily activities as well as sleeping at night.

4.2.4 Initial Skin Assessment
An Initial Skin Assessment Form was completed for each patient. The initial skin assessment comprised of a summary of each patient’s personal, genetic, and cancer construct together with a summary of the patient’s radiation therapy treatment and any other adjuvant therapy the patient may be on. The ability to accurately predict the likely severity of reactions would allow for a more individualised approach to skin care. Due to the small size of this cohort a correlation analysis was not performed but this was done in the final analysis of the larger 80 patient trial.

4.2.5 Serious adverse events
Mepilex-Lite dressings are promoted as an absorbent, self-adhesive dressings consisting of a thin, flexible sheet of hydrophilic polyurethane foam bonded to a water vapour-permeable polyurethane film backing layer. The contact surfaces of the dressings are coated with a soft silicone adhesive layer which does not contain any added chemicals. As there are no added chemicals, they are expected not to add or react with chemicals in or on the patient’s skin [23]. However, MacBride and colleagues [27] withdrew two patients from their case study when they experienced increased itching after the dressing was applied. These symptoms subsided once the dressing was removed. The authors suggested that the severe itching experienced by
these two patients may have been due to a radiation-induced skin reaction rather than the dressing itself. At the end of the current study, no serious adverse skin reactions were documented for the skin covered in Mepilex Lite dressings, which was similar to the study by Diggelmann et al. [24].
4.3 **Limitations**

Inherent in this study are certain characteristics of the design that impact on the interpretation of the study findings.

**Sample Size**

The most obvious limitation of small studies like this is the small cohort size as this limits the ability to draw descriptive or inferential conclusions about a larger group. This thesis only reports the results and analysis of thirteen patients who participated in the clinical trial at the Regional Cancer Treatment Services. However, despite the small sample size, the mean and the peak RISRAS scores for radiation-induced skin reactions showed decreases in the favour of Mepilex Lite dressings which were statistically significant. The final analysis with data from 80 patients from the four centres participating in the multicentre study has validated the findings of this smaller cohort and has allowed for the statistical analysis of the secondary objectives, which was not possible for this sub-cohort.

Travelling to Palmerston North Hospital for post-treatment skin assessments was the key reason only 13 patients were recruited during the recruitment period. The Regional Cancer Treatment Services serves a large geographical area and patients from Taranaki, Hawkes Bay, Napier and Gisborne would have to travel for at least three hours to get to the hospital and three hours to return back home. A total of 42 women were from these various regions and could not commit to the weekly travel commitment of the study design.

The weekly travel commitment outlined in the inclusion criteria may also have excluded elderly patients as they rely on volunteer drivers provided by the cancer society to drive them to the hospital for their daily treatments. Post-treatment, they no longer have access to these volunteer drivers and therefore would no longer be able to commit to the weekly visit to the researcher for skin assessments. This may also explain why only 61.5% of the participants within this cohort were aged 50 years.
and over which, when compared to the New Zealand’s nationwide breast cancer statistics, is much lower (70%) [4].

**Skin areas used for analysis**

The study design specified that the area of skin showing first sign of erythema on the post-mastectomy chest wall should be divided into two equal halves. Each half would then be randomised to either the treatment or the control arm using computer generated random numbers. Only one skin area per patient was included in the study because of statistical analysis considerations and choosing the very first patch to develop erythema was the most objective and consistent way to do this. However, other areas of the chest wall also developed erythema, some of these developed more severe reactions over time than the study area. In fact, the worst skin reactions were seen in the axilla regardless of whether they were dressed with Mepilex Lite, treated with aqueous cream, inside or outside the study area.

The skin in the axilla is subject to friction with the skin of the upper arm as well as from clothing. In addition, moisture from perspiration is likely to build up in this area, exposing the radiation-damaged skin to additional mechanical and chemical stress [44]. On the other hand, the skin on the chest wall is only subject to friction from clothing and can be reduced with loose outfits. Therefore, comparing the skin in these two locations is unfair as both these skin surfaces are subjected to different external factors which cannot be eliminated by intra-individual comparison or randomisation unless very large cohorts are involved. This trial clearly did not address the axilla problem, partially because the axilla was not part of the study area in most patients and partially because when it was included, the dressings did not stick well.

**Measurements**

Modified RISRAS scores were used to score radiation-induced skin reaction. An inherent limitation of any scoring tool including this tool is that it relies on visual assessment of skin reactions which is subjective to the interpretation of the researcher
Reflectance spectrophotometry objectively measures erythema by measuring the blood content of the dermal microvasculature [58, 59]. This method is expensive and only assesses a relatively small skin area (approx. 1 cm²) [60]. The validity of using digital photographic analysis was evaluated by Wengström et al. [60] who reported that utilizing digital images in combination with Adobe Photoshop program can provide a valuable method for ranking skin reactions with a high degree of precision during radiotherapy. Diggelmann et al. [24] took digital photographs at each skin assessment. However, even though every effort was made to standardize photographs, the quality of the photographs was such that no correlation was found between colour and RISRAS scores (PM Herst, unpublished results). The current trial did not use photographic analysis, as the primary objective of this trial was to evaluate moist desquamation. In addition, taking high quality photographs in four different departments would have been very challenging.

The Initial Skin Assessment required information of a patient’s personal construct such as nutritional status, sun exposure over the years, use of sun beds, etc. This reporting by patients is subject to both recall and report bias. Patients may not have been able to accurately remember this information over the years. Additionally, some patients may have preferred not to disclose information about a poor nutritional status such as smoking or excessive sun bed use due to the stigma associated with these lifestyle choices. To minimise these biases, the assessment was completed in combination with other sources including clinical notes as well as consultations with each patient’s radiation oncologist.

Skin surface dose estimations were done using the XiO planning system whereby the researcher placed interest points at specific places on the skin surface to obtain the dose. Plans with a bolus assigned often have high isodose lines concentrated on the skin surface and therefore moving the interest point only a few millimetres could show different doses making the dose output very subjective to the person placing the interest point on the “skin surface”. Furthermore, different window levels can make the patients’ skin contour appear slightly larger than others. For the purpose of
this study, the “soft tissue” window level was used. Additionally, the physics staffs have commented that the XiO planning system does not accurately depict the actual skin surface dose the patient will receive on treatment. However, the purpose of the skin dose estimations was to ascertain if the dose delivered under each patch was different statistically, not to determine the actual dose received by each skin patch. So, although the interest point doses may not depict the exact dose, it is still able to pick up any differences in the dose planned to each of the skin patches. Thermoluminescent dosimeters (TLDs) are a more accurate way to determine the actual dose delivered to the chest wall surface. TLDs were not utilized at the Regional Cancer Treatment Services due to resourcing issues. However, they were utilised on all patients at the Dunedin Oncology Centre who participated in the trial.

**Blinding**

This study was designed as an open trial where both the researcher and the patients were aware of the full treatment details. The difference between aqueous cream and Mepilex Lite dressings was apparent and as a result it was not feasible to blind patients. The inability to blind patients may have affected the participant component of the Modified RISRAS tool where the response criteria were subjective, such as pain and itchiness. There is strong evidence of a placebo effect in health research with patients who believed that they were receiving a new treatment showing some signs of improvement in symptoms. Blinding the patients would have reduced the risk of bias from this effect, giving perhaps a more truthful appraisal of the Mepilex Lite dressings.

Additionally, the researcher involved in skin observations was also fully aware which half on the study patch received which treatment. Thus, there is a possibility that the researcher may have subconsciously preferred one treatment over the other and their expectation of their preferred treatment may have influenced the RISRAS scoring. An independent RISRAS scorer who scored based on digital photographs could have addressed researcher bias. However, there are resource implications in ensuring each photograph for each assessment visit is reproduced under exactly the
same conditions for all the patients in the trial in four different centres. Another option for single blinding would be to have another researcher perform the RISRAS scoring. Patient would be educated about the importance of not disclosing to the second researcher the allocation of treatment on each half of their study patch. In the current trial these options were not pursued due to the lack of resources.

Compliance
Lack of compliance in covering the treatment skin patch with Mepilex Lite dressing would be an important determinant to the outcome of patient’s skin reactions. There was no satisfactory method of measuring compliance in patients from this cohort. To facilitate communication in the current study, each patient was asked if they wish to have an interpreter. Each patient was given a patient information sheet that they were encouraged to keep and refer to in order to follow the skin care instructions correctly. The instruction explained that the patients were expected to have one half of their skin covered by a dressing whilst the other parts will continue to be treated with cream. To further aid the patients in placing the Mepilex Lite dressings correctly, the exact location of the dressing was marked with a marker pen by the research assistant (the author) on the chest wall. This would assist patients to place the dressings in the same place when the dressings were removed for treatment each day or when the dressings had moved during daily activities. This was a problem for some of the patients who reported that the dressings moved during the day, particularly when they perspired a lot.

“Forgetfulness” was another cause for poor compliance for at least one of the patients (PLM06). There was no sure way of helping patients remember to put the dressings on when they were not in the department.
4.4 **Recommendations for Future Research**

Mepilex Lite dressings decreased the severity of radiation-induced skin reactions in this small cohort, which has now been validated by the analysis of all patients in the larger trial. In view of the limitations of this trial, further research study to determine the effectiveness of Safetac-based dressings could be done with the following improvements in the study design, measurements and blinding.

**Study Design**

It was evident from the current study results that dividing the area of the skin first showing erythema does not guarantee the worst affected skin would be captured in the study patch. A prophylactic study design would circumvent this problem. This would involve dividing the area of the chest wall to be irradiated into a medial and a lateral half (containing the axilla) and randomly allocate the dressings to either half from the start of radiation treatment, rather than at the first sign of erythema.

**Measurements**

RISRAS has been a valuable tool in this study as it provided a sensitive measure of radiation skin reactions and is highly recommended for future studies. However, the current study highlighted that during treatment, RISRAS scores obtained at least three times a week did not change significantly and hence future research studies can afford to reduce the frequency of these skin assessments. TLDs should be utilised when determining actual dose delivered to the skin in each arm of the study. Chest wall patients are often treated with bolus which is added using the treatment planning system after the planning CT scan has been done. The conformity of these boluses to the patients’ chest wall on treatment is often poor compared to what is seen on the treatment planning system and hence the actual dose delivered to the patients skin needs to be noted to predict severity of skin reactions.
Blinding

The benefits of having two researchers to introduce single blinding and reduce researcher bias are worth pursuing. Future studies should separate the person scoring the skin reactions to the person dealing with other aspects of patient care on a daily basis. Patients should be instructed to remove the dressings prior to their skin assessment and educated not to disclose to the observing researcher the status of each skin patch.
4.5 Conclusions

This is the first study that evaluated the effectiveness of Mepilex Lite dressings against standard aqueous cream across all stages of radiation-induced acute skin reactions. The trial was designed as an open label multicentre intra-patient controlled RCT. The findings of this small sub-cohort at Regional Cancer Treatment Services have provided evidence that Mepilex Lite dressings decrease the magnitude and the severity of all stages of radiation-induced acute skin reactions in women receiving post-mastectomy radiation therapy to their chest wall. The dressings also decreased the incidence of moist desquamation but did not affect the time to developing moist desquamation nor the time for moist desquamation to heal.

As the study used a randomised intra-patient controlled design, the results were not confounded by patient-related and treatment-related factors.

Notably, the patient component of the RISRAS score contributed substantially to the overall (combined) RISRAS score. The patient component of the modified RISRAS measures to what extent the irradiated skin reactions have affected the patient’s day to day activities. Since skin reactions are viewed as an unavoidable part of radiation treatment and management is directed towards the management of skin reaction symptoms [20], the patient RISRAS scores as well as the comments made by patients in the exit questionnaire regarding the ease of use and comfort provided by the dressings advocate the use of Mepilex Lite dressings in the clinical setting.

Lack of adherence of the Mepilex Lite dressing was identified as a disadvantage by some patients, particularly after the patients were advised to use aqueous cream under the dressings once a day when the skin appeared dry.

Future studies could incorporate the entire chest wall as the study area and use single researcher blinding in a prophylactic design.
In conclusion, Mepilex Lite dressings decreased the visual signs and discomfort associated with radiation-induced skin reactions, without causing further trauma and pain to the irradiated skin in this small sub-cohort of patients who received radiation therapy to their chest wall.


26. Graham, P., et al., *Randomized, paired comparison of No-Sting Barrier Film versus sorbolene cream (10% glycerine) skin care during postmastectomy irradiation.*


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, the irradiated area of your skin will be closely monitored. 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 local standard care. 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.

• 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.](image)

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 66I
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,

Hannah Thompson 06- 350 8430 ext: 7481
APPENDIX B: Informed Consent

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

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

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
- Pacific Islander

Iwi………………………………………………………….
Hapu……………………………………………………

- Fijian
- Indian
- Asian……………………………………………………
- Other (Please state)

Name: ________________________________
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Date:</td>
<td></td>
</tr>
<tr>
<td>Researchers</td>
<td>Dr Patries Herst (ph 04-3855475 ext 4753; mobile 027-3483945)</td>
</tr>
<tr>
<td>Signature</td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td></td>
</tr>
</tbody>
</table>
# APPENDIX C: Initial Skin Assessment Form

## Initial Skin Assessment

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

**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
Randomisation Fax Coversheet
Mepilex Lite for Radiation-Induced Skin Reactions Trial

Date ..............................
To: Dr Patries Herst  Fax: 04-3855375
Tel: 04-3855475
Email: patries.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 E: Exit Questionnaire

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)


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.
## APPENDIX F: Patient Demographics

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<tr>
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<th>PLM01</th>
<th>PLM04</th>
<th>PLM05</th>
<th>PLM06</th>
<th>PLM07</th>
<th>PLM08</th>
<th>PLM09</th>
</tr>
</thead>
<tbody>
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<td>29</td>
<td>71</td>
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<td><strong>Weight (Kg)</strong></td>
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<td>82</td>
<td>97</td>
<td>75</td>
<td>66</td>
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<td><strong>Separation (mm)</strong></td>
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<td>30</td>
<td>29</td>
<td>29</td>
<td>25</td>
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<td>Pakeha</td>
<td>Pakeha</td>
<td>Pakeha</td>
<td>Pakeha</td>
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<tr>
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<td>3</td>
<td>3</td>
<td>4</td>
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### CANCER CONSTRUCT

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<th>PLM07</th>
<th>PLM08</th>
<th>PLM09</th>
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</thead>
<tbody>
<tr>
<td><strong>Breast affected</strong></td>
<td>Right</td>
<td>Right</td>
<td>Right</td>
<td>Left</td>
<td>Left</td>
<td>Left</td>
<td>Left</td>
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<td>MFIDC</td>
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<td><strong>Stage</strong></td>
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<td>IIA</td>
<td>IIIB</td>
<td>IIIC</td>
<td>IIB</td>
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<td>IIIA</td>
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<td><strong>Grade</strong></td>
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<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
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<td>Pos</td>
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<tr>
<td><strong>PR</strong></td>
<td>Neg</td>
<td>Pos</td>
<td>Neg</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
<td>Pos</td>
</tr>
<tr>
<td><strong>HER2</strong></td>
<td>Neg</td>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Pos</td>
<td>Y</td>
<td>Y</td>
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### RT CONSTRUCT

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<th>PLM09</th>
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<tbody>
<tr>
<td><strong>Prescription</strong></td>
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<td>50Gy in 25#</td>
<td>50Gy in 25#</td>
<td>50Gy in 25#</td>
<td>40.05Gy in 15#</td>
<td>50Gy in 25#</td>
<td>40.05Gy in 15#</td>
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<td>6&amp;15MV</td>
<td>6&amp;15MV</td>
<td>6MV</td>
<td>6&amp;15MV</td>
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<td><strong>Fields</strong></td>
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<tr>
<td><strong>Bolus</strong></td>
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<td>Y</td>
<td>Y</td>
<td>Y</td>
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<td>Y</td>
<td>Y</td>
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<tr>
<td><strong>thickness (cm)</strong></td>
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<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.3</td>
<td>0.5</td>
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<tr>
<td><strong>Boost</strong></td>
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<td>N</td>
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<td><strong>Sclav Fields</strong></td>
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### THERAPY CONSTRUCT

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<th>PLM07</th>
<th>PLM08</th>
<th>PLM09</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgery</strong></td>
<td>Mastectomy</td>
<td>Y (Pre)</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td><strong>Axillary dissection</strong></td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td><strong>Chemotherapy</strong></td>
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<td>FEC</td>
<td>FEC</td>
<td>FEC</td>
<td>FEC</td>
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<tr>
<td><strong>Hormone Therapy</strong></td>
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<td>Y (Post)</td>
<td>Y (Post)</td>
<td>Y (Post)</td>
<td>Y (Post)</td>
<td>Y (Post)</td>
<td>Y (Post)</td>
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### CO-MORBIDITIES

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---

Pos= positive, neg=-negative; ALND, axillary lymph node dissection; ER, estrogen receptor; Her2, human epidermal growth factor receptor 2; MV, mega-voltage; PR, progesterone receptor; RT, radiation therapy. IDC= Infiltrating Ductal Carcinoma, MLC= Multiple Lobular Carcinoma, MCIDC= Multi-centric IDC, MFIDC= Multi-focal IDC, MIDC= Multiple IDC. Fitzpatrick Skin Type
### Appendix F patient demographic continued

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*Pos= positive, neg=negative; ALND, axillary lymph node dissection; ER, estrogen receptor; Her2, human epidermal growth factor receptor 2; MV, mega-voltage; PR, progesterone receptor; RT, radiation therapy. IDC= Infiltrating Ductal Carcinoma, MLC= Multiple Lobular Carcinoma, MIDC= Multi-centric IDC, MFIDC= Multi-focal IDC, MDC= Multiple IDC*
## APPENDIX G: Literature Review summary for recent Preventative Trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Patient Characteristics</th>
<th>Intervention/ Comparison</th>
<th>Sample Size</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Additional Comments</th>
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<tr>
<td>Theberge et al., 2009 [72]</td>
<td>RCT</td>
<td>Single-blind trial designed to test for inferiority</td>
<td>Breast or chest wall</td>
<td>Aluminum-free deodorant vs. no deodorant</td>
<td>n=84</td>
<td>RTOG NCI CTCAE (v3.0) used for pain &amp; pruritus. An in-house scale for sweating &amp; discomfort.</td>
<td>RTOG Grade 2 (axilla): Deodorant group - 23% No deodorant group - 30% <em>p</em>=.019 RTOG Grade 2 (breast): Deodorant group - 30% No deodorant group - 34% <em>p</em>=.049</td>
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<td>Bennett, 2009 [73]</td>
<td>RCT</td>
<td>Single-blind</td>
<td>Breast or Chest wall</td>
<td>Non-metallic deodorant vs. no deodorant Deodorant with mineral Tschermigite.</td>
<td>n=190</td>
<td>RTOG- Researcher and patient evaluated Questionnaire done on deodorant application</td>
<td>Researcher RTOG Grade 3 (axilla): Deodorant group - 6% NS No deodorant group - 1% NS Researcher RTOG Grade 2 (axilla): Deodorant group - 6% NS No deodorant group - 4% NS</td>
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<tr>
<td>Schmuth et al. (2002) [74]</td>
<td>RCT</td>
<td>Double blinded</td>
<td>Breast cancer</td>
<td>0.1% methylprednisolone and 0.5% dexamethasone vs. no tmt.</td>
<td>Meth = 10 Dex. = 11 control = 15 (untreated historical patients)</td>
<td>Clinical course, Adverse reactions, QOL In-house scale for skin Assessment</td>
<td>Mean severity score = 0.1 Meth arm = 2 patients reported itching Dex arm = 1 patient reported itching QoL for dexamethasone arm increase in depression, embarrassment, discomfort and limitations (<em>p</em> = 0.05). Average quality study Control was untreated historical cohort. Patients were randomised by being to any one arm. Power Calculation not done</td>
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<td>Shukla et al., 2006 [75]</td>
<td>Open label, RCT</td>
<td>Breast or Chest wall</td>
<td>Beclomethasone spray vs. No skin treatment</td>
<td>n=60</td>
<td>Erythema, dry desquamation &amp; moist desquamation. Endpoint – moist</td>
<td>Moist desquamation: Beclomethasone - 13.33% No treatment - 36.66% (<em>p</em>=0.0369)</td>
<td>Agent only applied to axilla. No patient comfort or QOL assessment. No power calculation.</td>
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<td>Study</td>
<td>Design</td>
<td>Department</td>
<td>Intervention</td>
<td>Sample Size</td>
<td>Outcome Measures</td>
<td>Findings/Comments</td>
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<tr>
<td>Omidvari et al., 2007 [76]</td>
<td>Double-blind, RCT</td>
<td>Post-mastectomy chest wall</td>
<td>Topical Betamethasone vs. vehicle emollient vs. no skin treatment</td>
<td>n=51</td>
<td>RTOG. Betamethasone 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. Low energy 120kV superficial x-ray machine used to deliver chest wall treatment. No patient comfort or QOL assessment.</td>
<td></td>
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<tr>
<td>Olsen et al.(2001)[80]</td>
<td>RCT</td>
<td>Single blinded</td>
<td>All RT patients except brain and gyno patients. Washing with soap vs. washing with soap and applying aloe vera.</td>
<td>Soap = 40, Aloe and soap = 33.</td>
<td>Erythema, skin texture, itch, tanning. RTOG. No significant difference in erythema rate (P = 0.948). Patients with light/moderate change in erythema: Aloe/soap: 75% Soap: 76%. Patient satisfaction not determined.</td>
<td></td>
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<tr>
<td>Heggie et al.(2002)[81]</td>
<td>RCT</td>
<td>Double blinded Intervention</td>
<td>Breast</td>
<td>Aloe vera vs aqueous.</td>
<td>Aloe vera = 107 Aqueous = 101</td>
<td>Itching, pain, erythema, dry and moist desquamation. In house assessment tool for itching, and moist desquamation. Dry Desquamation: P &lt;0.001 in favour of aqueous cream. Grade 2 pain greater in Aloe vera arm (P = 0.03). Itching: P &lt;0.05 in favour of aqueous cream. No significant difference in 2+ erythema score (p = 0.06) Patients with 2+erythema score: Aloe vera group: 51% Aqueous group: 66%. True randomisation, research nurse assessed skin toxicity,baseline measurements taken, reproducible methodology, inter-rater reliability scores calculated, independent outcome assessment.</td>
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<tr>
<td>Bosley et al.(2003) [82]</td>
<td>RCT</td>
<td>Most common diagnosis Hodgkin’s Disease</td>
<td>anionic polar phospholipid (APP)-based cream and vs. aloe vera-based gel</td>
<td>n=45</td>
<td>Patient-reported skin comfort. Researcher recorded dermatological assessments; Photographs weekly. APP showed a statistically significant advantage over Aloe vera for skin comfort and dermatological assessment variables. Small sample, unknown method of randomisation, concealment of allocation, blinding or handling of attrition.</td>
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<tr>
<td>Pommieret al.(2004)[84]</td>
<td>RCT</td>
<td>Single blinded</td>
<td>Breast</td>
<td>Trolamine topical agents, calendula</td>
<td>Trolamine = 128 Calendula = 126</td>
<td>Acute dermatitis grade 2 or higher RTOG Pain assessment done with Grade 2 or 3 41% calendula 63% Trolamine Four points in Trolamine group Power calculation done, patients stratified by skin type using Pathak scale,</td>
<td></td>
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</table>

**ALOE VERA**

- **Olsen et al.(2001)[80]**
  - RCT Single blinded
  - All RT patients except brain and gyno patients. Washing with soap vs. washing with soap and applying aloe vera.
  - Soap = 40, Aloe and soap = 33.
  - Erythema, skin texture, itch, tanning.
  - No significant difference in erythema rate (P = 0.948). Patients with light/moderate change in erythema: Aloe/soap: 75% Soap: 76%. Patient satisfaction not determined.

- **Heggie et al.(2002)[81]**
  - RCT Double blinded Intervention
  - Breast
  - Aloe vera vs aqueous.
  - Aloe vera = 107 Aqueous = 101
  - Itching, pain, erythema, dry and moist desquamation.
  - In house assessment tool for itching, and moist desquamation.
  - Dry Desquamation: P <0.001 in favour of aqueous cream. Grade 2 pain greater in Aloe vera arm (P = 0.03). Itching: P <0.05 in favour of aqueous cream. No significant difference in 2+ erythema score (p = 0.06) Patients with 2+erythema score: Aloe vera group: 51% Aqueous group: 66%. True randomisation, research nurse assessed skin toxicity,baseline measurements taken, reproducible methodology, inter-rater reliability scores calculated, independent outcome assessment.

- **Bosley et al.(2003) [82]**
  - RCT
  - Most common diagnosis Hodgkin’s Disease
  - anionic polar phospholipid (APP)-based cream and vs. aloe vera-based gel
  - n=45
  - Patient-reported skin comfort.
  - Researcher recorded dermatological assessments; Photographs weekly.
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- **Pommieret al.(2004)[84]**
  - RCT Single blinded
  - Breast
  - Trolamine topical agents, calendula
  - Trolamine = 128 Calendula = 126
  - Acute dermatitis grade 2 or higher RTOG Pain assessment done with Grade 2 or 3 41% calendula 63% Trolamine Four points in Trolamine group Power calculation done, patients stratified by skin type using Pathak scale,
<table>
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<tr>
<th>Study</th>
<th>Study Design</th>
<th>Location(s)</th>
<th>Intervention(s)</th>
<th>Comparator(s)</th>
<th>Sample Size</th>
<th>Outcome Measures</th>
<th>Main Findings</th>
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<td>Elliott et al. (2006)</td>
<td>RCT</td>
<td>Head and neck</td>
<td>Trolamine prophylactic arm = 166 Intervention trolamine arm = 175 Institutional preference = 165</td>
<td>Reducing incidence of high grade radiation dermatitis and improving QoL NCI-CTC@ v2.0 and ONS</td>
<td>n=69</td>
<td>Compared the median time to emergence of the first objective signs of radiation</td>
<td>Grade 2 or higher toxicity in each arm 79% Prophylactic arm 77% interventional trolamine arm 79% Institutional preference. No advantage of trolamine over best supportive care.</td>
</tr>
<tr>
<td>Ribet et al., 2008 [86]</td>
<td>RCT</td>
<td>Mainly breast cancer and head and neck cancer</td>
<td>Avène spring water gel vs. trolamine cream</td>
<td>443x495</td>
<td>n=69</td>
<td>Compared the median time to emergence of the first objective signs of radiation</td>
<td>No significant differences between the groups Multicentric</td>
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<tr>
<td>Gosselin et al., 2010 [87]</td>
<td>Double-blind, RCT</td>
<td>Breast</td>
<td>Trolamine (Biafine) vs. Aquaphore vs. RadiaCare vs. Placebo (water spray)</td>
<td>FASE CREAMS: N=208 RTOG. Home journal for participant self assessment.</td>
<td>n=208</td>
<td>RTOG. Home journal for participant self assessment.</td>
<td>No significant difference in minimising RTOG &gt;2 reactions. Patients preferred Trolamine (Biafine) for ease of application &amp; overall satisfaction.</td>
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<tr>
<td>Abbas &amp; Bensadoun, 2011 [61]</td>
<td>RCT</td>
<td>H&amp;N</td>
<td>Trolamine vs. Usual supportive care</td>
<td>RTOG. Primary endpoint – Grade 3 toxicity.</td>
<td>n=30</td>
<td>RTOG. Primary endpoint – Grade 3 toxicity.</td>
<td>RTOG Grade 3: Trolamine – 20% Control – 53.3% (p&lt;.01) Patients preferred Trolamine (Biafine) for ease of application &amp; overall satisfaction.</td>
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<tr>
<td>Wells et al.(2004)[70]</td>
<td>RCT</td>
<td>Breast, head and neck and anorectal</td>
<td>Sucralfate and no cream vs. aqueous Aqueous = 120 Sucralfate = 122 No cream = 124</td>
<td>Degree of reaction at week 5 RTOG^ Likert scale for itching and pain and other psychosocial factors.</td>
<td>n=120</td>
<td>Degree of reaction at week 5 RTOG^ Likert scale for itching and pain and other psychosocial factors.</td>
<td>Sucralfate vs. No cream groups compared No significant difference between groups Patients with RTOG mean score &gt;1: Sucralfate: 20%</td>
</tr>
</tbody>
</table>

**SUCRALFATE CREAMS**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Location(s)</th>
<th>Intervention(s)</th>
<th>Comparator(s)</th>
<th>Sample Size</th>
<th>Outcome Measures</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wells et al.(2004)[70]</td>
<td>RCT</td>
<td>Breast, head and neck and anorectal</td>
<td>Sucralfate and no cream vs. aqueous Aqueous = 120 Sucralfate = 122 No cream = 124</td>
<td>Degree of reaction at week 5 RTOG^ Likert scale for itching and pain and other psychosocial factors.</td>
<td>n=120</td>
<td>Degree of reaction at week 5 RTOG^ Likert scale for itching and pain and other psychosocial factors.</td>
<td>Sucralfate vs. No cream groups compared No significant difference between groups Patients with RTOG mean score &gt;1: Sucralfate: 20%</td>
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</tbody>
</table>

**RTOG Grade 3: Trolamine – 20% Control – 53.3% (p<.01) Patients preferred Trolamine (Biafine) for ease of application & overall satisfaction.**
No cream: 23%
No cream produced lower erythema readings than sucralfate and aqueous cream. Erythema readings also taken with a reflectance spectrophotometry. Power calculation done, results adjusted for smoking.

Falkowski et al., 2011 [90]
Open label, intra-individual comparison, non-randomised
Breast
Sucralfate cream vs. No cream
n=21
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.

OTHER TOPICAL AGENTS

Pardo Masferrer et al., 2010 [91]
Observational study with historical control
n=98
Breast
Ureadinb Cream vs. Historical control
n=98
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.

Roper et al., 2004 [92]
RCT
Open label,
Breast
Theta-Cream vs.
Bepantholi lotion (control)
n=20
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.

Graham et al.24(2004)[26]
RCT
Intervention type: Prophylactic
Breast cancer mastectomies
No sting barrier film (Cavilon) vs. sorbolene.
Total = 61
All points received both treatment types.
Rate of moist desquamation RTOG scale, Likert scale for pain and pruritus.
Reduction in the rate of RTOG skin score >2 (p = 0.049) with No-sting
Patients with RTOG skin score >2:
No sting group: 33%
Sorbolene group: 48%
Fairly good quality study. Study outcome not defined, power calculation done, true randomisation, well presented results.
Patient characteristic not defined for each treatment.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Patients</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vuong et al. (2004)[93]</td>
<td>Comparative Cohort study</td>
<td>Anal or gyno patients with concurrent chemotherapy</td>
<td>Silver nylon leaf dressing (SLND) Control group: Sulfadiazine used once reactions developed.</td>
<td>SLND = 15 Historical control = 15</td>
<td>Skin toxicity RTOG</td>
<td>Dermatitis scores significantly improved with SLND ($P &lt; 0.01$) Patients with &gt;grade 3 dermatitis score: SLND: 13% Sulfadiazine: 33%</td>
</tr>
<tr>
<td>Enomoto et al., 2005 [94]</td>
<td>RCT Double-blind</td>
<td>Breast</td>
<td>RayGel vs. Placebo gel</td>
<td>n=30</td>
<td>RTOG grade for each of 9 breast regions.</td>
<td>Mean whole breast RTOG grade was 24% lower in RayGel group. NS. Worst region grade was 14% lower in RayGel group. NS.</td>
</tr>
<tr>
<td>Coullert et al., 2007[95]</td>
<td>Blinded, RCT n=20</td>
<td>Breast</td>
<td>Topical wheat grass extract vs. Sorbolene (Control)</td>
<td>N=20</td>
<td>Oncology Nursing Society toxicity scoring system. Patient reported QOL.</td>
<td>No significant difference between groups although there was a trend towards increased time to peak incidence &amp; improved QOL in wheat grass group.</td>
</tr>
</tbody>
</table>

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. 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; 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 H: Literature Review summary for recent Management Trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Patient Characteristics</th>
<th>Intervention/ Comparison</th>
<th>Sample Size</th>
<th>Outcome Measures</th>
<th>Results</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HYALURONIC ACID</strong></td>
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<tr>
<td>Primavera et al., 2006</td>
<td>RCT</td>
<td>Breast or Chest wall</td>
<td>MAS065Da (HA based cream) vs. vehicle control (emollient)</td>
<td>n=20</td>
<td>NCI-CTC Skin (v2.0) Reflectance spectrophotometry. TEWL. Skin hydration using CorneometerTM. Patient symptoms (itch, pain) and preference.</td>
<td>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</td>
<td>Small sample size. No power calculated as pilot study. MAS065D randomised between left &amp; right side of breast/chest wall. Control emollient expected to have some benefit.</td>
</tr>
<tr>
<td>Leonardi et al., 2008</td>
<td>RCT</td>
<td>Breast</td>
<td>MAS065D (HA based cream) vs. vehicle control (emollient)</td>
<td>n=40</td>
<td>NCI-CTC skin (v2.0). VAS- itch, burning, pain. Patient evaluation of desquamation &amp; fatigue. Compliance.</td>
<td>NCI Grade &gt;2: MAS065D - 9% Control - 88.8% (p&lt;.0001) Burning in favour of MAS65D (p=.039) Pain, itch, dryness: NS Desquamation in favour of MAS65D (p=.02)</td>
<td>Small sample size. No power calculation Control emollient expected to have some benefit. Significantly improved skin reactions in MAS65D group.</td>
</tr>
<tr>
<td>Kirova et al., 2011</td>
<td>RCT</td>
<td>Breast or Chest wall</td>
<td>Hyaluronic acid (HA) vs. Placebo (emollient)</td>
<td>n=200</td>
<td>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.</td>
<td>No significant difference</td>
<td>Application of creams commenced at RTOG grade 1 dermatitis. Study power calculated. Intention to treat analysis. At baseline pain &amp; median colorimetric score were higher in HA group. MD not included as an endpoint or measure.</td>
</tr>
<tr>
<td><strong>TOPICAL HONEY</strong></td>
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<tr>
<td>Moolenaar et al., 2006</td>
<td>RCT</td>
<td>Breast or Chest wall</td>
<td>Honey gauze (HoneySoft) vs.</td>
<td>n=21 (24 areas randomised)</td>
<td>Primary endpoint: Closure of skin toxicity &amp; complete</td>
<td>Trend towards faster healing time and patient satisfaction in</td>
<td>Application of agents commenced at RTOG grade 1 dermatitis. Study power calculated. At baseline pain &amp; median colorimetric score were higher in HA group. MD not included as an endpoint or measure.</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Location</td>
<td>Treatment Groups</td>
<td>Sample Size</td>
<td>Outcome Measures</td>
<td>Findings</td>
<td></td>
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<tr>
<td>Shoma et al., 2010 [71]</td>
<td>RCT</td>
<td>Breast</td>
<td>Sulfadiazine cream plus oral pentoxifylline (PTX) [A] vs. Sulfadiazine plus local honey cream [B] vs. PTX plus dry dressing [C]</td>
<td>n=150</td>
<td>PCSA of burn.</td>
<td>Increased reduction in PCSA in groups B &amp; C at 12 weeks compared to group A (p&lt;.0001). Group C had shorter duration of treatment. Significant reduction in pain in group C. Significant improvement in movement in group C.</td>
<td></td>
</tr>
<tr>
<td>MacMillan et al. (2007)[102]</td>
<td>RCT</td>
<td>Anorectal (10), Breast (60) and head and neck (30).</td>
<td>Hydrogel (Intrasite) vs. dry dressing (Tricotex)</td>
<td>Dry dressing: 176 Hydrogel: 181</td>
<td>Time to heal (RTOG score of &lt;2)</td>
<td>100 (28%) developed moist desquamation 42 points from dry dressing and 58 points from gel dressing group Gel dressing healed more slowly (P = 0.03) No improvement in patient comfort.</td>
<td></td>
</tr>
</tbody>
</table>
| Gollins et al., 2008 [103] | RCT | Breast, chest wall or H&N | Hydrogel vs. Gentian violet (GV) | n=33 | 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.

**HYDROGEL DRESSING**

- **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.
### GENTIAN VIOLET

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Site</th>
<th>Dressing</th>
<th>n</th>
<th>Primary Endpoint</th>
<th>Results</th>
<th>Potential Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mak et al., 2005 [114]</td>
<td>Open label, RCT</td>
<td>Nasopharynx</td>
<td>Non-adherent absorbent dressing vs. GV</td>
<td>n=146</td>
<td>Healing of MD (days to complete re-epithelisation), Pain score, Mood disturbance, Neck mobility, Incidence of clinical infection</td>
<td>No significant difference in wound-healing time, mood disturbance, sleep, social interaction, appearance &amp; neck mobility. No patients developed an infection. Trend towards higher wound pain in GV group. NS.</td>
<td>Potential disadvantages of GV: dries out dermis, tissue-damaging, carcinogenic in animal studies &amp; impairs cell migration.</td>
</tr>
</tbody>
</table>

### SILVER LEAF DRESSING

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Site</th>
<th>Dressing</th>
<th>n</th>
<th>Primary Endpoint</th>
<th>Results</th>
<th>Potential Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vavassis et al., (2008) [105]</td>
<td>Single-blind, intra-individual comparison</td>
<td>H&amp;N</td>
<td>Silver leaf dressing vs. Silver sulfadiazine cream (Flamazine)</td>
<td>n=12</td>
<td>RTOG</td>
<td>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.</td>
<td>Application of dressing commenced at RTOG grade &gt;2. No mention of randomisation. Photographs taken &amp; 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.</td>
</tr>
</tbody>
</table>

### MEPILEX LITE DRESSINGS

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Site</th>
<th>Dressing</th>
<th>n</th>
<th>Primary Endpoint</th>
<th>Results</th>
<th>Potential Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacBride et al., 2008 [27]</td>
<td>Case study</td>
<td>Breast or H&amp;N</td>
<td>Mepilex Lite dressing</td>
<td>n=16</td>
<td>Modified RISRAS, Patient diary</td>
<td>Patient comfort increased with application of dressing.</td>
<td>Application of dressing commenced at RTOG grade 3 (confluent MD).</td>
</tr>
<tr>
<td>Diggelmann et al., 2010 [24]</td>
<td>RCT</td>
<td>Breast</td>
<td>Mepilex Lite dressing vs. Aqueous cream</td>
<td>n=24 (34 study areas)</td>
<td>Endpoint: occurrence of dry desquamation. Modified RISRAS. Surface skin temperature. Dose build-up.</td>
<td>Mepilex Lite dressing decreased extent of erythema (p&lt;.001). 71% preferred Mepilex Lite. No difference in skin surface temperature. Mepilex Lite has small bolus effect (0.5mm).</td>
<td>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.</td>
</tr>
</tbody>
</table>

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.
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