

Radiation skin reactions

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INTRODUCTION

Radiation skin reactions are, to some extent, an inevitable consequence of radical radiotherapy, particularly where skinfolds are present. Although the widespread use of linear accelerators has reduced the severity of skin reactions through more sophisticated skin-sparing techniques, the increased use of concomitant chemotherapy and high-dose radiotherapy means that skin reactions can still be a significant problem for patients. There are surprisingly few data describing the patient's experience of skin reactions, and much conflicting evidence exists as to how skin reactions should be prevented, minimised and managed. Practice across UK radiotherapy departments reveals considerable inconsistency and a lack of evidence on which to base skin management decisions.

THE AETIOLOGY OF RADIATION SKIN REACTIONS

Although radiation skin reactions cannot be understood without an appreciation of the radiobiological effects of radiotherapy treatment, it is also important to consider the way in which healthy skin regenerates. The skin is composed of two main layers: the epidermis (superficial layer) and the dermis (deep layer), as shown in Figure 8.1.

Sitton (1992) describes the process in which skin homeostasis is normally achieved. As superficial cells are shed through normal desquamation, new cells are formed in the basal layer of the epidermis, and these continually replace those that are lost. The dermis, which contains blood vessels, glands, nerves and hair follicles, provides the supportive structure required for the epidermis to renew. Repopulation of the entire epidermis takes approximately 4 weeks, although this process can be shorter during times of healing.

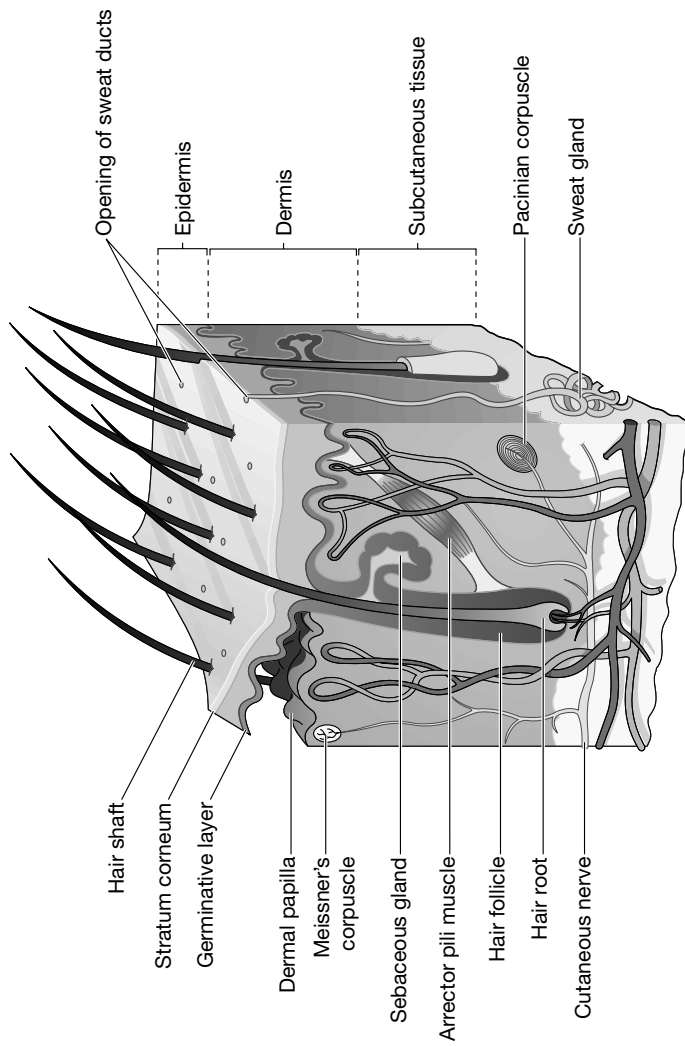


Figure 8.1 The skin, showing the main structures in the dermis. (Reproduced with permission from Waugh & Grant 2001.)

In general, the basal layer of the epidermis proliferates rapidly, so it is particularly sensitive to radiotherapy (see Ch. 5). Ionising radiation essentially damages the mitotic ability of clonogenic or stem cells within the basal layer, thus preventing the process of repopulation and weakening the integrity of the skin. Radical radiotherapy repeatedly impairs cell division within the basal layer, and so the degree to which a skin reaction develops is dependent on the survival of actively proliferating basal cells in the epidermis. Moist desquamation occurs when clonogenic cells in the basal layer are sterilised, thus rendering cells unable to repopulate in time to replace the damaged tissue. Consequently, the epidermis becomes broken (Glean et al 2001, Hopewell 1990).

Archambeau et al (1995) found that basal cell loss began once the radiation dose reached 20–25 Gy, and that maximum depletion of basal cells occurred when the patient had received a dose of 50 Gy. In practice, this means that skin reactions tend to become visible around the second to third week of radical radiotherapy, reaching a peak at the end or within 1 week of completion of treatment (Arimoto et al 1989, Ratliff 1990). Interestingly, Archambeau et al (1995) found that by the time higher doses of up to 60 Gy had been absorbed, repopulation of basal cells had occurred, so that levels were similar to those existing prior to radiotherapy.

The majority of skin reactions will have healed within 4 weeks of completion of treatment (Rezvani et al 1991). 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 (Hopewell 1990). Healing becomes visible as islands of epidermal cells expand and reform in central and peripheral regions of the desquamation (Cox et al 1986). Initially, this reformed skin may be hyperpigmented, due to stimulation or destruction of melanocytes as a result of exposure to radiation (Cox et al 1986, Ratliff 1990).

Skin reactions can range from mild erythema, through dry desquamation (dry, flaky or scaly skin) to confluent moist desquamation, where blistering, peeling and sloughing of the skin occur. The most severe stage of necrosis is rarely seen nowadays. At any one time, it is possible to see a combination of erythema, dry and moist desquamation within a single treatment field. Although relatively short lived, skin reactions are uncomfortable and itchy, can be painful and are sometimes dose-limiting (Campbell & Illingworth 1992, Munro et al 1989). The symptom distress associated with radiation skin reactions is particularly poorly researched.

INCIDENCE OF RADIATION SKIN REACTIONS

It is difficult to estimate the true incidence of skin reactions, given that most departments do not systematically record their occurrence or severity. A survey carried out in the early 1990s reported that more than 80% of UK radiotherapy departments frequently saw skin reactions, although these were not usually severe (Barkham 1993). The research literature supports an approximate incidence of erythematous reactions in 80–90% of patients, and a relatively low incidence of moist desquamation at around 10–15%. However, as most incidence figures are drawn from populations of patients involved in clinical trials, it is difficult to assess how much these figures are affected by the products or techniques under

evaluation. One recent descriptive study of patients receiving radiotherapy to the breast reported that only 4–8% of women had no reaction at all, but fewer than 10% had moist desquamation by the completion of treatment (Porock & Kristjanson 1999). Clinical experience confirms that skin irritation and discomfort are common in patients being treated radically, and that moist desquamation reactions can be extremely difficult to manage, as well as being distressing and painful for the patient.

ASSESSMENT OF RADIATION SKIN REACTIONS

The many systems for categorising radiation skin reactions have been neatly summarised by Noble-Adams (1999a). Most include four or five stages, ranging from mild erythema to necrosis, and these form the basis of many assessment tools. The Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer. (RTOG/EORTC) score (Table 8.1) is probably the most widely used in practice and research. This score makes a useful distinction between faint erythema and tender, bright erythema, as well as between patchy and confluent moist desquamation. One limitation of the RTOG scoring system is that dry desquamation and faint erythema are scored equally, although they may not be equal in severity from the patient's point of view. Radiotherapy to the brain or head and neck can produce severe dry desquamation, in which thick scales develop on the scalp or neck, described by some patients as like 'crocodile skin'. The appearance of faint erythema is completely different, yet the RTOG score attributes the same score to both reactions. Similarly, an equal score is given to bright erythema and patchy moist desquamation. Because of this, many researchers have modified the four criteria to create a subdivision of score 2, thus allowing for a distinction to be made between the two (Porock et al 1998, Westbury et al 2000).

An additional limitation of the RTOG is that the scoring system only measures the appearance of the skin from the point of view of the clinician, thus giving no indication of how the patient feels. Weekly skin assessments performed by patients and clinicians have demonstrated a consistent tendency for healthcare providers to underrate the severity of skin reactions when compared with patients (Williams et al 1996). The Radiation-Induced Skin Reaction Assessment Scale (RISRAS) developed by Noble-Adams (1999b) addresses this problem. This scale,

Table 8.1 RTOG/EORTC acute radiation scoring criteria – skin

0	1	2	3	4
No change over baseline	Follicular, faint or dull erythema; epilation; dry desquamation; decreased sweating	Tender or bright erythema, patchy moist desquamation; moderate oedema	Confluent, moist desquamation other than skinfolds, pitting oedema	Ulceration, haemorrhage, necrosis

RTOG, Radiation Therapy Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer.

Reproduced with permission from Cox et al (1995).

designed for weekly use, incorporates a patient-rated symptom scale and a health-care professional assessment scale (see Fig. 8.2 for the latest version).

One of the advantages of this scale is that it allows an accurate estimate of the *area* of skin affected. It also recognises that the severity of the skin reaction within a treatment area is not uniform, i.e. a patient may have a very small area of moist desquamation and a large area of bright erythema or dry desquamation. Noble-Adams (1999c) evaluated the RISRAS by asking 19 experts to assess a series of clinical photographs using the tool. Although there were some outlying responses, the overall interrater reliability coefficient was fairly high, at 0.70.

In clinical practice, the use of assessment tools such as the RISRAS are a vital component of supportive care. Systematic weekly assessment would provide excellent data on the experience of patients and the development of skin reactions, as well as guide the management of symptoms and wound healing. In clinical research, however, such tools are open to criticism because of their lack of objectivity.

Over the past few years, a variety of 'objective' skin measurement techniques have been reported in the literature. Probably the most clinically applicable technique is that of reflectance spectrophotometry, used for a number of years in dermatology settings and now gaining interest as a reliable method of measuring erythema in irradiated skin (Denham et al 1995, Simonen et al 1998). It is believed to measure the blood content of the dermal microvasculature and, as such, is sensitive to the vasodilatory effects thought to occur as a result of epithelial cell death during radiotherapy.

The erythema meter, used to take such measurements, is a compact (but expensive) piece of equipment. A probe 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. The degree of erythema in different areas of the treatment field can be measured, and 'control' measures can also be taken outside the field. The meter is able to detect subclinical erythema and is thus considerably more sensitive than the naked eye. Studies that use reflectance spectrophotometry demonstrate that invisible but measurable erythematous reactions occur at very low doses of radiation (Simonen et al 1998), perhaps explaining why some patients appear to experience skin discomfort at an earlier stage than is thought to be related to their radiotherapy. Recent experience of using the erythema meter in a clinical research setting suggests that there are some practical difficulties associated with the technique, although the trial is still in progress, so data have not yet been analysed (MacMillan et al personal communication).

Other measurement techniques include ultrasound (Warszawski et al 1998) and dielectric constant measurements (Nuutinen et al 1998). The latter technique is based on the hypothesis that radiation damage produces a change in free and bound water molecules within the skin; the dielectric constant is related to the tissue water content of the skin. Although these techniques may provide vital objective data, they are unlikely to be adopted for everyday clinical use.

RISK FACTORS FOR RADIATION SKIN REACTIONS

A number of factors appear to influence the severity, onset and duration of radiation skin reactions. In general, moist areas of the body or those that contain skinfolds are more likely to be affected, for example, under the breast, axilla, head

Patient symptom scale

Symptoms	Not at all	A little	Quite a bit	Very much
Do you have any tenderness, discomfort or pain of your skin in the treatment area?	1	2	3	4
Does your skin in the treatment area itch?	1	2	3	4
Do you have a burning sensation of your skin in the treatment area?	1	2	3	4
To what extent has your skin reaction and your symptoms affected your day-to-day activities	1	2	3	4

Health care professional scale

Record of treatment details included here (dose, fractions, etc.)

Erythema (E)	0 (normal skin)	1 (dusky pink)	2 (dull red)	3 (brilliant red)	4 (deep red-purple)
Dry desquamation (DD)	0 (normal skin)	1 (<25%)	2 (>25–50%)	3 (>50–75%)	4 (>75–100%)
Moist desquamation (MD)	0 (normal skin)	1.5 (<25%)	3.0 (>25–50%)	4.5 (>50–75%)	6.0 (>75–100%)
Necrosis (N)	0 (normal skin)	2.5 (<25%)	5.0 (>25–50%)	7.5 (>50–75%)	10 (>75–100%)

Ongoing assessment scale

Date	No.	E	DD	MD	N	Pain	Itch	Burn	Activities	Total
Treatments:										

Instructions for use

1. Assess the patient as often as you feel is appropriate.
2. Rate erythema by recording the degree of colour change.
3. Rate dry desquamation, moist desquamation and necrosis by evaluating the proportion (%) of the treatment area affected by that particular reaction.
4. Record your gradings on the ongoing assessment scale.
5. Ask the patient to fill out the patient symptom scale and record the scores on the ongoing assessment scale.
6. Total the scores.

Figure 8.2 The Radiation-Induced Skin Reaction Assessment Scale (RISRAS). (Courtesy of R. Noble-Adams.)

and neck, perineum and groins (Crane 1993, Dische et al 1989, Farley 1991, O'Rourke 1987). Intrinsic factors may also play a part, including the baseline characteristics of the patient in terms of general skin condition, nutritional status, age, general health, comorbid disease and ethnicity (Blackmar 1997, Porock & Kristjanson 1999, Sitton 1992). Extrinsic factors, including the dose, energy and fractionation regime (i.e. those *prescribed* by the radiotherapist), also affect the degree of skin reaction experienced. Although the skin-sparing effect of modern linear accelerators ensures that the maximum dose of radiotherapy is reached *below* the basal layer of the skin, certain treatment techniques will increase the likelihood of the skin receiving a dose sufficient to cause a visible reaction. These include:

- the application of skin bolus (tissue-equivalent material such as wax) which is used to 'build up' the skin to ensure that a higher dose is administered to a particular area, e.g. a scar
- the use of tangential fields in breast cancer treatment. These are radiation fields which include an area of sloping skin, so that higher doses are likely to be received by skin within the 'thinner' area
- the use of parallel opposed fields where the two skin surfaces are proximal, e.g. in the treatment of laryngeal tumours
- the use of electrons, which are less penetrating than megavoltage irradiation. Sitton (1997) explains that, whilst linear accelerators deliver about 20–30% of the radiation dose to the skin, electron beam energies can deliver between 85 and 98%.

The increasing use of chemoradiotherapy also affects the severity of skin reactions experienced. The main principle of chemoradiotherapy is that the two treatments work synergistically so as to improve overall response. The other side of the coin is that radiation side effects tend to be exacerbated by the addition of chemotherapy (O'Rourke 1987, See et al 1998). Increased skin sensitivity following chemotherapy is also seen: indeed, a recall phenomenon may occur when adjuvant chemotherapy is given after completion of radical radiotherapy (Ratliff 1990, Sitton 1992). In these cases, an area of skin demarcated by the radiation field turns red and can become itchy several months after the end of radiotherapy. Cytotoxics commonly associated with an increased potential for skin reactions are dactinomycin, doxorubicin, methotrexate, 5-fluorouracil, hydroxyurea and bleomycin (O'Rourke 1987, Sitton 1992). Newer drugs such as paclitaxel have also been reported to induce 'radiation recall' (Phillips et al 1995).

However, even within a group of similar patients treated with an identical radiotherapy regime, considerable variation in skin toxicity can be seen. The nutritional status and frailty of the patient are certainly known to influence wound healing. Additionally, it has always been claimed that skin reactions could be induced or exacerbated by the application of perfumed products or substances containing metal elements (for instance, creams containing zinc or silver). A small number of studies have examined prognostic factors in patients with breast cancer, but there is no evidence to explain the nature and pattern of skin reactions in other treatment groups.

Porock et al (1998) investigated potential predictive factors for radiation skin reactions in 126 patients with breast cancer, using a conceptual framework

developed from previous research, clinical knowledge and experience. A modified RTOG score and a visual analogue scale were used to measure degree of skin reaction and pain experienced at weekly intervals during radiotherapy. All women taking part in the study received a dose of 45 Gy over 5 weeks, followed by a 20 Gy electron boost to the lumpectomy scar over 2 further weeks. Patients most commonly reached a maximum RTOG score of 1 (indicating faint or dull erythema), but at the 5-week time point, between 25 and 50% of patients had developed tender or bright erythema or moist desquamation. Those areas of the breast most likely to develop severe skin reactions were the axilla, inframammary fold and sternum. Univariate and logistic regression analysis revealed that a number of variables appeared to be predictive of severe skin reactions (defined as RTOG ≥ 2). Figure 8.3 illustrates the conceptual framework of predictors of radiation skin reactions used as a basis for the study.

The predictive factors identified by Porock et al (1998) illustrate the point that a group of patients receiving very similar radiotherapy treatment may experience very different side effects. The results of the study confirm a dose-response relationship, in that patients who had received higher doses (of 45 Gy) were more likely to have a severe skin reaction in the upper quadrants of the breast, where the majority of breast cancers are located. Other interesting predictors of skin reaction were also revealed.

Weight and bra size

The authors suggest that heavier patients with large breasts are more prone to developing skin reactions because they require a greater radiation dose to the skin,

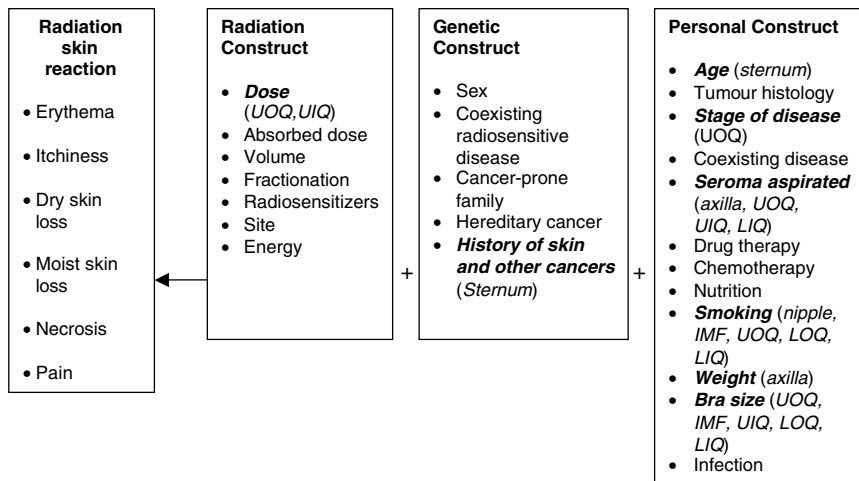


Figure 8.3 Conceptual framework of predictors of radiation skin reactions. UOQ, upper outer quadrant; UIQ, upper inner quadrant; LIQ, lower inner quadrant; LOQ, lower outer quadrant; IMF, inframammary fold. Italics show variables predictive of severe skin reactions. Specific treatment sites for which these variables were predictive are given in parenthesis. (Adapted with permission from Porock et al 1998.)

and because their potential to heal may be compromised by reduced vascularity in adipose tissue. Additionally, such patients are more likely to experience friction and moisture in the axilla and inframammary fold, where more severe skin reactions are seen.

Smoking

The significance of smoking as a highly predictive variable relates to the reduced ability of cells to reoxygenate during radiotherapy, as well as the adverse effects of nicotine on wound healing, in particular, cutaneous vasoconstriction.

Seroma aspiration

Interestingly, those patients who had required aspiration of a seroma following their breast surgery appeared to be more likely to develop a severe skin reaction. Porock et al hypothesise that damage to the lymphatic system was more likely in these patients, and that this would compromise wound healing during radiotherapy.

Stage

Porock et al patients with larger tumours (stage II) had probably experienced more trauma to surrounding tissues during surgery, and thus might have a reduced potential for wound healing.

History of skin cancer

The authors suggest that this predictor was related to previous exposure to or greater sensitivity to ultraviolet radiation (particularly as this study was carried out in Australia), although they are unable to explain why this factor was not predictive in all sites of the breast. It is possible that patients who had sunbathed in a bikini or bathing costume were more likely to have exposed their sternum than other areas of their breast, but this can only be speculation.

Age

It was found, unexpectedly, that increased age actually predicted for less severe skin reactions around the sternum. As increasing age generally results in an impaired ability to heal, the authors offer an alternative explanation for this finding. They suggest that the older patients were less likely to have received chemotherapy, and that this might have affected the degree of skin reaction they experienced.

Although the work of Porock et al (1998) requires further testing; it provides those working in radiotherapy with crucial evidence on which to base the assessment and prediction of skin reactions, so that care can be planned appropriately.

PATTERN OF ERYTHEMA

Observations made more than 60 years ago demonstrated that some patients experience a transient 'primary erythema' of the skin within hours of radiotherapy. Data from a recent study (Simonen et al 1998) suggest that the development of erythema *may* occur in two phases: the first peak is within 10 days of treatment, and the second is approximately 20 days into treatment. The findings of Simonen et al suggest that a clear dose-response relationship may not exist and that two different inflammatory responses are produced. It appears that the first occurs as a result of the direct release of substances known to cause vasodilation (such as prostaglandins). Doses as low as 1.5 Gy may be enough to produce this effect. The corresponding 'dip' in erythema is caused by the development of refractoriness to further erythematous stimuli, and possibly by an active vasoconstrictive process. This dip is followed by a second inflammatory response occurring as a result of mediators released in response to epithelial cell death.

This second inflammatory response appears to intensify as treatment progresses. Several studies support the fact that radiation skin reactions peak towards the end of radiotherapy, usually between 5 and 6 weeks (King et al 1985, Porock et al 1998, Westbury et al 2000). In King et al's study (1985) more than 80% of patients receiving chest or head and neck irradiation reported skin irritation by the last week of treatment, and this was the most common symptom experienced at this stage.

There are very few qualitative data available in the literature to describe the experience of skin reactions. Patients do, however, experience considerable distress as a result of skin damage, as these quotes illustrate.

Didn't just get redder, it erupted ... it was one great big scabby thing ... like it had been burnt ... you see these people on television who've been burnt, you know that's all cracked, it was like that

(patient with cancer of the larynx who developed a skin reaction after treatment was completed).

I stripped off a load of skin here, I can't feel this at all anyway and I hadn't realised it had got stripped off – it was all bleeding and raw

(patient describing what had happened as a result of washing and shaving his radiotherapy site following a parotidectomy, which had left him with superficial numbness of his cheek and jaw).

My breast is so uncomfortable and painful. I am doing everything I should and it is not improving. The doctor warned it could be like this but I didn't expect it to be so bad. I don't think having radiotherapy was such a good idea.

Had very little sleep owing to pain from the burn on the side of my breast.

Didn't go to church because I didn't want people looking surreptitiously at my burns

(Wells 1995, 1998).

WASHING

The freedom and ability to wash as and when you wish is a basic human need. Evidence now confirms that gentle washing during treatment does no harm, yet recent surveys have shown that some radiotherapy departments still advise patients not to wash their treatment sites for the duration of radiotherapy, or have restricted washing policies (Glean et al 2001, Lavery 1995). The idea of being unable to wash your face and neck, armpit or perineum for up to 6 weeks is at best uncomfortable and at worst positively unhygienic. Not washing may in fact promote skin infection as well as cause distress and reduce social acceptability. Three randomised trials have assessed the effect of washing on skin reactions, and all have concluded that washing is *not* associated with more severe skin reactions and that refraining from washing may in fact be detrimental (Campbell & Illingworth 1992, Roy et al 2001, Westbury et al 2000).

Campbell & Illingworth (1992) found no statistically significant differences in severity of skin reactions between those who washed with water alone and those who washed with soap, but did demonstrate that skin reactions were worse when patients were not allowed to wash at all. Westbury et al (2000) examined the role of hair washing for patients undergoing radical doses of radiotherapy for brain tumours, and concluded that the group who were randomised to no hair washing had marginally more severe symptoms 6 weeks into treatment. Unlike the previous trial, this study did attempt to measure symptom distress, finding that patients were upset by not being able to wash their hair, although the severity of symptoms was not significantly affected. The study by Roy et al (2001) found that symptoms improved in the group who were allowed to wash, and that they were also significantly less likely to develop moist desquamation. All three studies highlight the difficulties of ensuring patient compliance with professional advice, suggesting that personal experience and beliefs may have a significant influence on washing behaviour during radiotherapy. These findings reinforce the importance of patient education, supported by written information materials.

MANAGEMENT OF SKIN REACTIONS

Erythema

Surveys demonstrate that the management of skin reactions across the UK is inconsistent, and that even within hospitals and departments, practice can vary (Boot-Vickers 1999, Glean et al 2001, Lavery 1995, Thomas 1992). It is also true to say that the evidence base for practice is particularly scarce. There are relatively few published protocols and guidelines for the management of skin reactions, although many departments have developed their own and some consensus is slowly being achieved. Four recent protocols (Boot-Vickers 1999, Campbell & Lane 1996, Glean et al 2001, Mallett et al 1999) advocate a simple skin care regime, including the following advice:

- gentle washing, using mild unperfumed soap (or shampoo) and warm water
- avoidance of friction by patting the skin dry with a soft towel, and wearing loose cotton clothing

- use of a simple moisturiser, e.g. aqueous cream, either throughout treatment or when erythema develops
- avoidance of perfumed skin products, deodorants and make-up
- use of an electric razor instead of wet shaving
- protecting the skin from wind, sun and extreme temperatures
- 1% hydrocortisone cream for itchy areas

Only one author provides the sensible advice that patients with intact skin may swim during radiotherapy, provided the skin is rinsed afterwards and aqueous cream applied (Boot-Vickers 1999).

In clinical practice, there is probably a reasonable consensus about the use of simple moisturisers to relieve skin discomfort and erythema. Recently published work tends to advocate the application of creams or lotions from the first day of radiotherapy, but this is not yet routine practice in most departments, where such agents are usually reserved for symptom relief once erythematous reactions are manifest or, indeed, only when the prescribed therapy is complete. Some departments still advocate the use of powders such as talcum or cornstarch (Farley 1991), although these may in fact dry the skin and produce worse reactions as a result of the build-up effect and the blocking of sweat glands or hair follicles. Certainly, by the time the skin cracks or breaks down, powders tend to collect in messy clumps and are thought to establish a medium for fungal infections, serving no other useful purpose.

Although steroid creams such as hydrocortisone 1% may be useful to treat itching, they may also mask superficial infection and should therefore be used with caution. Lavery (1995) pointed out that there were no data to illustrate that steroid creams effectively reduce progression to moist desquamation. Similarly, there is no evidence base for the use of antibacterial creams such as Terra-Cortril ointment (hydrocortisone and tetracycline), nor is there any theoretical benefit for such creams in the absence of proven infection. However, a small study published by Simonen et al (1998) found that topical steroids do appear to reduce erythematous reactions. Hydrocortisone 1% cream appeared to modify the inflammatory response occurring during the second peak of erythema, whereas indomethacin 1% spray had no effect. Interestingly, both topical agents had been discontinued before the second peak of erythema occurred, suggesting that hydrocortisone may have a delayed effect.

In recent years, a number of research studies have investigated the application of topical agents such as ascorbic acid, or moisturising creams with active ingredients, such as sucralfate, hyaluronic acid, aloe vera gel and starch-containing creams (Table 8.2). It may be that simple emollients such as aqueous cream are just as effective as those with active ingredients, but again, little evidence exists to support this theory.

Two products have recently aroused interest, due to their potential to stimulate cell activity and growth: sucralfate and hyaluronic acid. Sucralfate has mainly been used in the treatment of gastric ulcers. It is an aluminium salt that adheres to proteins within the ulcers, thus providing a barrier to further breakdown (Delaney et al 1997). It also appears to stimulate cell growth by increasing prostaglandins and epidermal growth factor, enhancing epithelial circulation and acting as an anti-inflammatory agent (Maiche et al 1994). A number of studies have suggested

Table 8.2 Summary of research studies investigating the prevention or management of radiation-induced erythema (in chronological order)

Skin care approach evaluated	Authors	Method/strength of evidence (no. of evaluable patients/site of treatment)	Results	Endpoints/clinical outcomes
Chamomile and almond oil	Maiche et al (1991)	Physician-blinded RCT (50/breast). Chamomile cream and almond oil randomly applied above or below scar	No significant differences between areas above or below scar. Skin changes appeared later in chamomile group. Patients preferred consistency and application of chamomile cream	Four-point score for skin reaction; pain; itching
Washing	Campbell & Illingworth (1992)	RCT (99/breast or chest wall). Water alone vs soap and water vs no washing	Washing (with or without soap) diminished erythema and itching compared with no washing	RTOG scores. Itch; pain; compliance
Bioshield foam	Dini et al (1993)	Prospective evaluation (38 women with mixed sites). Bioshield only	Disappearance of symptoms (58%), improvement (37%)	Visual analogue scales, observer-rated four-point scale
Topical ascorbic acid	Halperin et al (1993)	Blinded RCT (65/brain). Ascorbic acid solution vs placebo	No benefit associated with topical ascorbic acid	Five-point skin and hair loss scales
Sucralfate cream	Maiche et al (1994)	Double-blind RCT (50/breast or chest wall). Sucralfate vs base cream	Mild reactions appeared later in sucralfate group (statistically significant at 5 weeks) Itching improved in sucralfate group	Five-point rating scale. Prevention of erythema; rate of recovery; patient preference (including cosmetic properties)
Silicone-coated polyamide net Mepitel	Adamietz et al (1995)	Prospective evaluation (21/mixed group)	No significant effects on skin reaction, but well tolerated Increased radiation dose detected under dressing, but no associated increase in skin reaction	Radiation dose measurement at skin surface Skin reaction under dressing rated on six-point scale

Continued

Table 8.2 (Continued) Summary of research studies investigating the prevention or management of radiation-induced erythema (in chronological order)

Skin care approach evaluated	Authors	Method/strength of evidence (no. of evaluable patients/site of treatment)	Results	Endpoints/clinical outcomes
Bepanthen cream	Lokkevnik et al (1996)	RCT (79/breast or larynx) cream vs no cream	No benefits to using cream	Scoring criteria based on RTOG
Aloe vera gel	Williams et al (1996)	2 RCTs (breast and chest wall) double-blind; aloe vera gel vs placebo (194); aloe vera gel vs no treatment (108)	No difference between groups Some patients experienced an allergic reaction to aloe vera	Toxicity score (patient and physician). Maximum reported severity of erythema, time to occurrence of severe erythema; duration of severe erythema
Sucralfate cream	Delaney et al (1997)	RCT (39/head and neck, breast, other) Sucralfate cream vs base cream	No significant differences	Time to healing; area of moist desquamation; pain relief; adverse effect
Superskin liquid polymer skin sealant	Goebel & Hazuka (1997)	Prospective non-comparative evaluation (54/breast, head and neck)	31% developed patchy moist desquamation (4% confluent) 65% developed redness with itching or tenderness. 'Apparent' delay in time to skin toxicity	Daily symptom record Five-point weekly score for erythema; desquamation; ulceration; pigmentation; sensitivity to touch; epilation
Hyaluronic acid cream	Liguori et al (1997)	RCT (134/breast, head and neck, pelvis) Hyaluronic acid vs placebo	Significantly less severe reactions in hyaluronic acid group between treatment weeks 3 and 8 Improved healing time in intervention group	Six-point skin toxicity score Healing time
Usual skin care regime	Meegan & Haycocks (1997)	Prospective comparative study using consecutive samples (156/breast). Group A (92) warm water only. Group B (64) usual skin care	No significant differences	Four-point skin toxicity score. Discomfort; use of analgesics; interference with normal activities

Homeopathy (belladonna 7 cH and X-ray 15 cH)	Balzarini et al (2000)	Double-blind RCT (66/breast) Homeopathy vs placebo	No significant differences, although total severity score suggested benefits with homeopathic treatment	Skin colour; heat; oedema; pigmentation; frequency and severity of skin reaction
Biafine wound dressing emulsion	Fisher et al (2000)	RCT (172/breast) Biafine vs best supportive care (usually aloe vera or aquaphor)	No statistically significant differences, although may reduce postradiation toxicity in large-breasted women	Prevention of skin toxicity. RTOG/EORTC + Oncology Nursing Society criteria; quality of life; patient satisfaction
Hair washing	Westbury et al (2000)	RCT (109/brain). No hair washing vs normal hair washing	No significant differences	RTOG (modified) Distress; frequency of hair washing; pain; itching
Aloe vera gel	Olsen et al (2001)	Blinded RCT (73/chest, head and neck, pelvis) Soap and aloe vera gel vs soap alone	Skin reactions later in aloe vera group, once cumulative radiotherapy dose > 27 Gy	Time to first observed skin change RTOG Skin change variables includ- ing age, ethnicity, skin type, texture, itch
Washing	Roy et al (2001)	RCT (99/breast) Washing with soap vs no washing	Significantly less moist desquamation in washing group and trend towards decreased symptoms	RTOG scores Pain; itching; burning

RCT, randomised controlled trial; RTOG, Radiation Therapy Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer.

that sucralfate may reduce radiation mucositis in the gut, and these are discussed in Chapter 9 and 10. Two randomised studies have investigated the effect of sucralfate cream in the prevention and management of radiation skin reactions (Maiche et al 1994, Delaney et al 1997). Maiche et al's study of 50 patients receiving electron beam therapy to the chest wall following mastectomy found that grade 2 skin reactions (dark, painful erythema) were significantly less common ($P = 0.05$) in the areas treated with sucralfate, and that skin reactions also recovered more quickly. A smaller study assessed the effect of sucralfate on moist desquamative reactions (Delaney et al 1997). No significant differences in discomfort or skin healing were detected, although the small sample size may partially explain the lack of statistical significance. Unfortunately, neither of the studies assessed patient comfort in any detail, nor did they address the question of whether the placebo cream was more effective than applying no cream. At present, sucralfate cream is not commercially available in the UK.

Only one study has assessed the role of hyaluronic acid cream on the development of skin reactions (Liguori et al 1997). This natural polymer is found in the dermis, where it plays a key role in the healing process by stimulating fibrin, granulocyte and macrocyte activity, and inducing proliferation of fibroblasts. Liguori et al randomised 134 patients with breast, head and neck and pelvic cancers to receive hyaluronic acid cream or placebo cream to their treatment site from the first day of therapy. The placebo group suffered more severe erythema, more moist reactions and slower healing times than the hyaluronic acid group. Statistically significant differences in severity of reactions were consistently found between week 3 and week 8 of treatment. This study provides promising evidence that hyaluronic acid may improve healing in established skin reactions as well as prevent reactions happening in the first place. However, other than a physician's assessment of tolerability of the creams, this study also fails to assess the patients' perceptions of their skin reaction and its associated distress. Hyaluronic acid cream is not currently commercially available in the UK.

Moist desquamation and wound care

It is difficult to estimate with any confidence the number of individuals who will experience moist desquamation, as this information is rarely collected systematically. The risk of developing a moist skin reaction increases as higher doses are absorbed, and other factors referred to in the section on risk factors, above, also play a part. Patients undergoing concomitant chemotherapy are also more likely to experience moist desquamation (O'Rourke 1987), as are those whose treatment affects areas where skinfolds rub together. Recent studies indicate that between 2 and 10% of patients (Fisher et al 2000, Porock & Kristjanson 1999) develop confluent moist desquamation during treatment. However, clinical experience shows that a number of patients develop moist reactions once treatment is over, and it is quite possible that we are not aware of the full extent of the problem.

The management of moist desquamation poses a particular challenge, not least because reactions often develop in awkward areas such as the axilla, neck and perineum, where dressings cannot easily be applied. The evidence to support the use of wound care products for moist desquamative reactions is scarce, and this

remains an area of considerable controversy (Barkham 1993, Glean et al 2001, Lavery 1995). In their review of the literature, Glean et al (2001) found that, between 1979 and 1999, only eight randomised controlled trials evaluating skin products were reported.

Old-fashioned methods of drying the skin were shown to be popular with around 60% of departments surveyed by Thomas (1992). Many practitioners still favour the exposure of skin reactions to the air, using cool hairdryers or even oxygen as a means of keeping the skin dry. The application of antiseptic agents intended to dry the skin also remains relatively common, in particular the use of povidone-iodine spray, proflavine lotion (Thomas 1992), and gentian violet (Mak et al 2000). Lavery's survey (1995) reported that 63% of radiotherapy centres were still using gentian violet, despite the fact that it had been withdrawn from clinical use because of its carcinogenic properties. Other centres continue to advocate the use of combination creams containing steroid and antibiotic agents, or the application of antiseptic creams such as Flamazine, used in the treatment of burns (Atkinson 1998, Cameron 1997). However, research into the care of general wounds has long since demonstrated that the application of antiseptics to wounds confers little advantage to irrigation with saline, due to the transient nature of the antiseptic contact, the inability to effect a reduction in bacterial count and the increased risk of sensitivity reactions (Lavery 1995, Thomas 1992). There is also controversy over the use of creams that contain metallic ions (e.g. Flamazine), due to the potential for scatter of the radiation beam during treatment. This may however, present a purely theoretical concern (Thomas 1992).

Simple dressings alone, such as non-adherent layers or tulle, are not recommended, due to the pain and trauma caused at dressing changes (Glean et al 2001). Latterly there has been increasing interest in the use of dressings such as hydrocolloids, hydrogels and alginates, which provide the ideal moist wound-healing environment. These dressings have been widely researched in burns care and their role and function ascertained (Atkinson 1998). The evidence base for the management of first-degree burns with epidermal damage is much more robust, and healthcare professionals working in radiotherapy could learn a great deal from this literature (Atkinson 1998, Lavery 1995).

Thomas (1992) found a general lack of knowledge of wound care and suggested that healthcare professionals fail to appreciate the benefits of new products coming on to the market, despite these being based on the latest scientific evidence. Staff working in radiotherapy have certainly been slow to accept the virtues of moist wound-healing theory. However, considerably more research is required to demonstrate the effectiveness of newer wound care products for moist desquamation reactions. It is important that clinical trials comprehensively address issues of healing, patient comfort, pain reduction, prevention of infection and minimal trauma to wounds on dressing removal. Dressings must be readily conformable to awkward areas, able to absorb varying amounts of serous leakage associated with epidermal damage without macerating surrounding skin, and must be removed without disturbing granulation. In the radiotherapy setting, hydrogels appear to have much to offer due to their easy application, conformability, rehydration and cooling properties (Williams 1997). Most do, however, require secondary dressings and a means of holding them in place that does not compromise skin integrity. Although flexible netting tubes (such as Netelast) are a versatile means of securing

Table 8.3 Summary of research studies investigating the management of established skin reactions or moist desquamation

Skin care approach evaluated	Authors	Method/strength of evidence (no. of evaluable patients/site of treatment)	Results	Endpoints/clinical outcomes
Tegaderm	Shell et al (1986)	Pilot RCT (21/breast)	Trend towards faster healing time, reduction in discomfort	Time to healing; rate of healing/efficacy; discomfort
DuoDERM	Margolin et al (1990)	Non-comparative evaluation (20/breast, mixed group)	No wound infections. Mean healing time 12 days 83% of patients reported their comfort to be excellent or good	Infection; wound, oral and skin surface temperature; patient satisfaction with comfort, adhesion, containment of gel and aesthetic acceptability
Second Skin hydrogel dressing Gentian violet	Pickering & Warland (1991)	Prospective evaluation (19/breast) Patients alternately assigned to one or other treatment	60% complete relief of symptoms (Second Skin) vs 33% (gentian) Time to healing 4–6 days (mean 4.6) in Second Skin group and 5–22 days (mean 11) in gentian group	Relief of symptoms (pain, irritation, movement restriction, sleep disturbance, duration); time to healing; infection
Vigilon/Second Skin	Crane (1993)	Prospective evaluation, case study (4/breast)	Reduced pain and discomfort with hydrogel dressing	Comfort
Sucralfate cream	Delaney et al (1997)	RCT (39/head and neck, breast, other) Sucralfate cream vs base cream	No significant differences	Time to healing; area of moist desquamation; pain relief; adverse effects. Daily symptom record
Hydrocortisone and neomycin ointment DuoDERM dressing (control gel formula)	Chen et al (1997)	RCT (105/nasopharynx) steroid ointment vs normal saline vs gel dressing (DuoDERM)	Reduced healing time in steroid ointment group (21–28 days) and gel dressing group (7–14 days) vs normal saline (30–35 days). Only 15% in both groups satisfied with pain relief (cf. 95% in gel dressing group). Fewer local infections in gel group	Healing time; bacterial growth; pain relief

Dermofilm dressing	See et al (1998)	Prospective evaluation (50/breast, head and neck, pelvis, other)	98% gained significant symptom relief Healing time medians between 11 and 16 days	RTOG score Size of wound; healing Diary of symptoms
Various dressings and topical agents	Porock & Kristianson (1999)	Prospective descriptive study (126/breast)	Bepanthen cream found to be soothing but sticky and staining; fixomull (Mefix) improved comfort, pain and itching	RTOG (modified) Pain
Gentian violet Hydrocolloid dressing	Mak et al (2000)	Prospective RCT (39 patients; 60 wounds/nasopharynx)	No significant differences in healing. Wound size significantly smaller in gentian group; trend towards higher pain severity in hydrocolloid group; better comfort and aesthetic acceptance in hydrocolloid group	Wound size; pain, infection; time to healing; patient satisfaction

RCT, randomised controlled trial; RTOG, Radiation Therapy Oncology Group.

dressings, they can feel tight and hot to wear and are not tolerated by all patients. Other products use the body temperature to encourage adherence, e.g. Tielle, and these may be of value if they can be removed with little or no trauma, using water or saline. One interesting approach to wound care contradicts the generally accepted rule that no adhesive dressings or tape should be applied to skin within a treatment area. Porock & Kristjanson (1999) report the successful use of dressing tape such as Mefix applied to skinfold areas and left in place to *prevent* friction during treatment. Another early study (Shell et al 1986) found that adhesive moisture vapour-permeable dressings (Tegaderm) were effective at reducing healing time, and could be removed easily with the aid of baby oil.

Surveys have repeatedly shown that different departments apply conflicting and even contradictory principles to their wound care practice (Glean et al 2001, Lavery 1995, Thomas 1992). The paucity of evidence inevitably contributes to this problem. Table 8.3 summarises research studies that have been conducted on wound care products and techniques designed to manage established or moist skin reactions.

It is important that future research studies also consider the potential for dressings to *prevent* moist desquamation from occurring, for instance the use of hydrogels in brisk erythema/dry desquamation (Crane 1993), or Mefix tape to minimise friction where skin surfaces touch (Porock & Kristjanson 1999). A vital consideration is the cost-effectiveness of dressings, as modern products are often more expensive than their traditional counterparts. Their use in non-radiotherapy settings is usually justified on the basis of their remaining in place for several days, but moist desquamation reactions often require once- or twice-daily dressing changes to ensure adequate cleansing and comfort. Although this may be costly, sceptics of new dressings should be reminded that the application of unproven preparations may be just as cost-ineffective (Lavery 1995).

The latest guidelines issued by the College of Radiographers (2001) recommend hydrocolloid dressings for light to moderately exuding wounds such as patchy moist desquamation. These are both flexible and comfortable, providing a slight cushioning effect. However, most are adhesive, thus limiting the opportunity for regular skin assessment, and some are relatively thick, which could theoretically introduce a 'bolus' effect. Two studies have evaluated such dressings, but do report some practical problems associated with their use. Margolin et al (1990) found that occlusive hydrocolloid dressings appeared to reduce healing time, but were also prone to leakage – a problem often experienced with the use of these dressings in skinfold areas such as groins and buttocks. Mak et al (2000) compared the effects of a hydrocolloid dressing with gentian violet on the healing of moist desquamation wounds. The study failed to achieve statistical significance in terms of healing times, but found that wound sizes were significantly larger in the hydrocolloid group. At first glance, this appears to be a negative finding, but it may just reflect the fact that moist wound-healing products tend to promote the debridement of damaged tissue as well as the granulation of new tissue. This phenomenon also appears to occur with hydrogels, and it is important that healthcare professionals are not dissuaded from their use because of a transient increase in wound size. Mak et al's study provided a clear indication that patients found the hydrocolloid to be more comfortable and aesthetically pleasing. In contrast, those who received gentian violet commented on the skin remaining tight and dry, a feature they disliked.

The recent guidelines (College of Radiographers 2001) recommend alginate sheets for confluent moist desquamation. Their rationale is that these dressings not only convert to a hydrophilic gel on contact with the wound, lending them conformity in difficult areas, but they also encourage granulation and have haemostatic properties, which can be an advantage in areas of exposed skin. One relevant practical issue is that dressings will usually need to be removed for radiotherapy treatment, to reduce the possibility that the additional 'volume' of the dressing provides a 'bolus' effect and thus increases the dose to the skin. Thilmann et al (1996) used thermoluminescence dosimetry techniques to determine the dose increase to skin during radiotherapy with electrons and high-energy photons. Dressings tested included a silicone-coated wound dressing made of polyamide, a silk acetate dressing, a self-adhesive hydrocolloid dressing and an alginate wound dressing. These authors concluded that the use of dressings during electron therapy does not significantly increase the dose administered to skin. However, they recommend that, when using high-energy photons, only 'extremely thin' dressings are permissible, and then only when there is no 'aggravated skin reaction' (p. 181). They also emphasise the need to ensure that the dressing is accounted for in calculating the applied dose. It is also important to be aware that some products, such as silver-impregnated charcoal, contain metallic ions, which may be associated with radiation scatter.

Although the development of moist desquamation may prompt radiotherapy staff to consider the suspension or early completion of radiotherapy, it is not desirable to allow gaps in treatment, due to the potential for these to affect outcome (Hendry et al 1996). If the use of a comfortable, pain-relieving dressing can enable treatment to continue, all disciplines should work together to ensure that compliance is achieved.

One aspect of care which is not covered by the recent guidelines is that of the systemic management of symptoms associated with radiation skin reactions. Although comfortable dressings can largely relieve these symptoms, some patients experience significant pain, itching or infection which cannot be adequately managed by topical agents. It is important that the patient's need for pain management is assessed, and appropriate analgesia prescribed and evaluated. Non-steroidal anti-inflammatory drugs can often be extremely effective, and can also relieve the discomfort associated with itching and swelling around the skin reaction. Antihistamine tablets can be useful in the management of severe itching, although caution must be taken in relation to the drowsiness these can produce. If infection is suspected, appropriate wound swabs should be taken, so as to establish whether antibiotic or antifungal therapy is required. Timely management of infection can rapidly reduce the discomfort and intensity of a severe skin reaction.

CONCLUSION

Radiation skin reactions remain a significant problem for patients undergoing radical treatment. Wide variations in practice continue to exist, and there is patently a need for more research into skin and wound care products both to prevent and manage skin reactions.

Existing variations in practice suggest that the use of protocols and guidelines has much to offer, if we are to improve consistency in care (Boot-Vickers 1999,

Campbell & Lane 1996, Mallett et al 1999). A two-pronged approach that combines the conduct of research studies to enhance the evidence base with the translation of research findings into practice through protocols and guidelines has to be the way forward.

Patient information is of course an essential component of care. It is crucial that healthcare professionals work together to ensure that a consistent approach to skin care is adopted in their treatment centre. Patients must be adequately informed about the risks of skin breakdown, the self-care strategies they can employ to minimise problems and the potential for skin reactions to worsen once treatment is over. While it remains difficult to predict exactly who will develop moist desquamation, some groups are clearly identifiable as being at increased risk, and experienced healthcare professionals can often judge who is liable to further skin breakdown. If adequate end-of-treatment assessment takes place, patients whose skin is at risk can be referred to community staff and appropriate wound care planned. Skin reactions can be a particularly distressing side effect of treatment, not just because of the pain and discomfort, but also because of the 'unsightly' and 'dirty' nature of these reactions, and the disruption that is caused to daily lives. It is vital that we not only take on board new evidence of wound-healing principles, but also that we listen and respond to the symptom distress caused by radiation skin reactions.

SUMMARY OF KEY CLINICAL POINTS

- Radiation-induced skin reactions are a common side effect of radical treatment, and may become more so as further combined chemoradiotherapy regimes are introduced.
- Radiation skin reactions are a cause of considerable distress and discomfort to patients and are also difficult to manage.
- Damage to the basal layer occurs at doses of around 20–25 Gy or approximately 10 days into radical treatment.
- A number of risk factors exist, including intrinsic and extrinsic factors, which may predispose a patient to developing a skin reaction.
- Skin reactions tend to peak towards the end of treatment, and frequently worsen after treatment is completed.
- There are limited data available on the patient's experience of skin reactions and associated symptoms.
- The management of skin reactions has, until recently, been ritualistic and preference-led, rather than based on current wound-healing evidence.
- Consistent patient information is vital, as are the commitment and collaboration of the multidisciplinary team in radiotherapy.
- Systematic regular assessment of skin reactions is important, and a number of useful tools exist to guide this assessment.
- Washing the skin with or without soap during treatment has been proven not to be detrimental.
- Moisturising creams and those with active ingredients may prevent the onset and severity of erythema, but more research is needed in this area.
- Moist wound-healing methods are gaining support in the management of moist desquamation, but more evidence of their effectiveness is required.

- Most existing research studies are small and have evaluated a range of obscure products not readily available in the UK.

Recent published guidelines provide a sound basis for evidence-based supportive care. Whilst definitive evidence for and against certain dressings and skin products is still unavailable, the management of radiation skin reactions should be guided by the optimisation of patient comfort.

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