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Retrospective study of radiotherapy-induced skin reactions in breast cancer patients: Reduced incidence of moist desquamation with a hydroactive colloid gel versus dexpanthenol

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A B S T R A C T

Purpose: Dermatitis is a very frequent and distressing side effect of radiation therapy that may necessitate a treatment interruption when evolving towards more severe forms such as moist desquamation (MD). The aim of this study was to compare the efficacy of two topical agents, a dexpanthenol cream vs a hydroactive colloid gel combining absorbing and moisturising properties, in preventing MD in breast cancer patients.
Methods: This retrospective study compared two successive groups of breast cancer patients undergoing radiotherapy after breast-sparing surgery between 2008 and 2012. A group of 267 patients applied a 5% dexpanthenol cream on the irradiated zone throughout the course of their radiotherapy. Another group of 216 patients applied first the dexpanthenol cream then replaced it by the hydroactive colloid gel after 11–14 days of radiotherapy. Radiation treatment (total dose, technique, and equipment) was the same for the two groups. The clinical outcomes were the occurrence and time to onset of moist desquamation.
Key results: The overall incidence of MD was significantly lower in patients who applied the hydroactive colloid gel (16%) than in those who applied the dexpanthenol cream (32%, odds-ratio = 0.35). Also, MD occurred significantly later with the hydroactive colloid gel than with the dexpanthenol cream (hazard ratio = 0.39).
Conclusions: Compared with the dexpanthenol cream, the hydroactive colloid gel significantly reduced the risk of developing MD in patients undergoing radiotherapy for breast cancer. These promising results warrant further research on the efficacy of hydroactive colloid gels in managing radiation dermatitis.

Introduction

Skin reaction or dermatitis is a frequent side effect of radiation therapy, affecting up to 95% of cancer patients treated with radiotherapy (McQuestion, 2011). They can occur as acute or late side effect of radiotherapy (i.e., within or beyond 90 days of treatment) with various degree of severity, depending on multiple factors that can be intrinsic (i.e., patient-related) or extrinsic (i.e., treatment-related). For instance, intrinsic factors include breast size or the sensitivity of the exposed region (e.g., large breasts and body regions containing skin folds, such as the groin, are more susceptible to skin reactions). Extrinsic factors include the total radiation dose and the dose delivered per fraction (the onset and severity of skin reactions being dose-related) or the concurrent use of other cancer therapies (see for example Porock, 2002). Typically, acute radiotherapy-induced skin reactions manifest within 2–3 weeks of radiotherapy, peak towards the end, and heal within a month after completion of therapy (Wells and MacBride, 2003). They are graded by severity on a continuum ranging from dryness or red rashes (irritation or mild erythema) and dry desquamation (itchy, peeling skin) to more severe moist desquamation (painful, sloughing skin blisters with serous exudate) and ulceration.

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Managing radiotherapy-induced skin reactions, also known as radiation dermatitis or radiodermatitis, represents a major clinical challenge to radiotherapy departments. First, skin reactions are particularly distressing to patients and can seriously affect their quality of life (Munro et al., 1989). Second, as skin reactions evolve towards more severe dermatitis such as moist desquamation, they might lead to a reduction of the delivered doses or even an interruption of radiation treatment that can negatively influence treatment outcome (Feight et al., 2011). Therefore, skin care is an essential function of the radiation team. However, to date, there is no consensus among radiotherapy departments on how radiodermatitis should be prevented or treated (Salvo et al., 2010). Although several guidelines and recommendations have been published (e.g., Bolderston et al., 2006; Feight et al., 2011; Glean et al., 2001; McQuestion, 2011; Wong et al., 2013), little evidence-based protocols have been developed and many departments still apply a treatment policy based on clinical experience and anecdotal evidence, leading to a great variability in clinical practice (e.g., D'Haese et al., 2005; Harris et al., 2012).

In our institution, the standard skin care protocol for breast cancer patients undergoing radiotherapy includes the application of a topical agent on the irradiated zone throughout the course of the radiation treatment. For many years our institutional preference was an oil-in-water emulsion containing 5% dexpanthenol (Bepanthol® Cream, Bayer AG, Leverkusen, Germany). Dexpanthenol is an alcohol analogue of pantothenic acid (a provitamin known to accelerate and improve wound healing by promoting epithelial formation and regeneration) that acts like a moisturizer when used topically and reduces itching and irritation (Biro et al., 2003). Later on, another product was introduced in our institutional skin care protocol to prevent the development of moist desquamation: after 12 days of radiotherapy, at fraction 13, the dexpanthenol cream was replaced by a hydroactive colloid gel (Flamigel®, Flen Pharma NV, Kontich, Belgium). (Since this gel is delivered by the nurses, a fixed starting point was chosen to facilitate the implementation of the new practice routine; day 13 corresponding to the middle point of the period during which skin reactions generally develop.) This gel combines the moisturising and absorbing properties of hydrocolloids and hydrogels (hydrocolloids maintain optimal tissue hydration by absorbing exudates, while hydrogels restore optimal tissue hydration by donating moisture to the wound). Combining these properties enables the interaction with the wound bed to maintain an optimal moist environment, which accelerates wound healing, reduces pain, and prevents desiccation, scars, and infection (e.g., Field and Kerstein, 1994). As they can regulate the moisture of the wound bed, hydroactive colloid gels can be recommended for both dry and exuding skin wounds (Korting et al., 2011), what makes them particularly suitable for the management of radiodermatitis. Moreover, they present the additional advantage of being easy to use and to remove and do not necessarily require secondary dressing or additional taping, which reduces the discomfort, irritation, or tissue damage commonly associated with dressing changes. Finally, their cooling effect on the skin attenuates sensations of pain and burning (Ferreira Alves et al., 2009). Such advantages are not negligible because they alleviate patients' discomfort, pain and irritation – aspects that also ought to be taken into account in skin care practice (McQuestion, 2011).

Dexpanthenol has shown beneficial effects on a wide range of skin disorders (Ebner et al., 2002) but evidence regarding its efficacy in preventing or managing radiation dermatitis is lacking (e.g., Feight et al., 2011). For instance, Løkkevik et al. (1996) found no clinically important benefits of applying dexpanthenol (vs no treatment) for managing skin reactions in laryngeal and breast cancer patients. In fact, in its latest guidelines, the Skin Toxicity Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) found insufficient evidence to support the efficacy of dexpanthenol and therefore recommended against its prophylactic use (Wong et al., 2013).

In the wound care literature, hydrocolloid or hydrogel dressings are commonly recommended for the management of minor acute cutaneous wounds, superficial to partial thickness burns, or chronic wounds (such as diabetic foot lesions or pressure ulcers), with beneficial effects on healing rates, infection, and pain (e.g., Chaby et al., 2007; Singh et al., 2004; Wasiak et al., 2013). The past decade, hydrocolloid and hydrogel dressings have also increasingly emerged in the radiodermatitis literature and in clinical practice (e.g., Harris et al., 2012), though their effectiveness is far from being established (for reviews see for example Kedge, 2009 or Wong et al., 2013). Yet formulations that combine moisturising and absorbing properties (as gels, not as dressings) are virtually absent in studies to date, in both the radiodermatitis and the wider wound care literature. A few case reports documented the use of a hydroactive colloid gel on recalcitrant wounds (among which a burn wound of the perineum following radiotherapy) and reported beneficial effects in terms of healing, pain relief, comfort, and ease of application (Panasiti et al., 2006; Van den Plas et al., 2009). Also, a randomized controlled trial evaluating the efficacy of a hydroactive colloid gel on burn wounds found significant benefits in terms of healing rates and pain relief (Yang et al., 2013; available in abstract form only). But to our knowledge, only one study investigated the effect of such a hydroactive colloid gel on acute radiodermatitis (Huang et al., 2005; available in abstract form only). In this randomized controlled trial, 60 patients receiving radiotherapy for head and neck cancer were assigned to either the hydroactive colloid gel or the routine clinical practice from the onset of skin reactions. The authors compared healing rates and the incidence of grade $\geq$3 skin reactions (scored according to the Radiation Therapy Oncology Group – RTOG – grading tool, grade 3 corresponding to confluent moist desquamation and grade 4, to ulceration and necrosis). They found significant differences in favour of the hydroactive colloid gel, with higher healing rates (83% vs 47% for routine clinical practice) and a lower incidence of severe skin reactions (10% vs 33% for routine clinical practice). Thus hydroactive colloid gels seem to be potentially promising for the management of acute radiation dermatitis but to date the available data is insufficient to draw firm conclusions regarding their efficacy.

The objective of this study was to compare these two topical agents in managing acute radiation dermatitis. More specifically, we retrospectively compared the effect of the dexpanthenol-containing emulsion and the hydroactive colloid gel on the incidence and time to onset of radiotherapy-induced moist desquamation in two successive cohorts of breast cancer patients.

Materials and methods

Participants

This retrospective study was approved by the local Medical Ethics Committee, as required by our institutional policies, and was thus conducted in compliance with ethical regulations.

The study population consisted of women treated in our radiotherapy department for invasive or non-invasive breast adenocarcinoma during the past four years. In an attempt to control for extrinsic risk factors and maximize homogeneity between the patients, strict inclusion and exclusion criteria were applied: Patients were considered for inclusion if they had undergone breast-sparing surgery and completed conventional radiation therapy with an irradiation fractionation regime of 25 daily fractions of 2 Grays (Gy) to the whole breast (five times a week) followed by a 16-Gy boost (in 2-Gy fractions) to the tumour bed. Adjuvant hormone

therapy or (neo-)adjuvant chemotherapy was allowed. Brachytherapy boost was excluded as there is a three-week delay before the delivery of the boost (in contrast to standard, external boost, which is administered immediately after the last fraction to the whole breast). Other exclusion criteria were metastatic disease, mastectomy surgery, concomitant chemoradiotherapy, and use of tissue compensators ("bolus") during radiotherapy.

Furthermore, following our skin care practices of that time, patients must have used the dexpanthenol cream either throughout their radiotherapy or until day 12, after which the hydroactive colloid gel was started. Unfortunately, in many cases, patients did not start using the hydroactive colloid gel at fraction 13, mainly due to nurses' mistakes (or omissions) or to logistical reasons (i.e., stock shortage). So, in order to maximize sample size, we decided to broaden our criteria and to include the patients who started using this gel 11–14 days after the start of radiotherapy.[1] Finally, information on skin reactions (i.e., onset of moist desquamation) had to be registered so that sufficient data were available for review.

A total of 483 consecutive patients treated between July 2008 and December 2011 met these criteria and were included in this retrospective study. Of these, 267 patients applied the dexpanthenol cream (Bepanthol® Cream) on the irradiated area three times per day from the start until completion of radiation therapy (hereafter referred to as the dexpanthenol group). The remaining 216 patients applied the dexpanthenol cream from the start of radiation therapy three times per day then, after 11–14 days, replaced it by the hydroactive colloid gel (Flamigel®, three times per day) until completion of radiotherapy (hereafter, the hydroactive group). Except for this, skin care protocol remained the same throughout the study period. For instance, patients were asked to follow general skin care recommendations such as gently washing with mild soap or non-soap cleansers; patting dry with a soft towel instead of rubbing; wearing soft, loose clothing; and not to use perfumed creams or lotions on the irradiated area.

Radiation therapy

All patients received a total irradiation dose of 66 Gy (25 + 8 2-Gy fractions) and none of them required bolus. The same radiation equipment was used for all patients. Radiotherapy was planned using the Eclipse™ treatment planning system (version 10.0, Varian Medical System, Palo Alto, CA) and treatment was delivered by applying two tangential photon (half) beams set up isocentrically (with or without additional segmental fields), using a 4 MV (Siemens Mevatron MX-2, Siemens Inc, USA) or 6 MV linear accelerator (Siemens Primus or Clinac® DHX, Varian Medical Systems, Palo Alto, CA). The second series of boost was delivered using either photon (4 MV or 6 MV) or electron beams (9–15 MeV).

Data collection and study endpoints

During radiotherapy, the date of onset of moist desquamation (MD) was recorded for each patient (the skin was assessed by the oncology nurses according to the World Health Organization criteria for grading acute cutaneous toxicities, 0: no changes, 1: erythema, 2: dry desquamation, 3: MD, 4: necrosis; World Health Organization, 1979).

For the retrospective analysis, data collection included: (1) time to onset of MD (as a function of received cumulative radiation dose, in Gy); (2) breast size (measured by breast diameter, calculated as the distance, in cm, between the two entrance points of the photon beams); and (3) whether chemotherapy had been administered prior to radiotherapy. In this case, the time interval between the end of chemotherapy and the start of radiotherapy (in days) was recorded as well.

Endpoints were the occurrence and time to onset of MD.

Table 1
Characteristics of the two groups of patients.

	Dexpanthenol ($N = 267$)	Hydroactive ($N = 216$)	p
Mean age (SD), years	57.81 (12.08)	57.74 (11.71)	0.949
Radiation energy level[a]			0.993
n (%) 4 MV	120 (44.94%)	97 (44.91%)	
n (%) 6 MV	147 (55.06%)	119 (55.09%)	
Mean breast size[b] (SD), cm	20.68 (3.01)	21.14 (3.09)	0.102
n (%) small breasts (diameter < 20 cm)	117 (43.82%)	78 (36.11%)	
n (%) large breasts (diameter ≥ 20 cm)	150 (56.18%)	138 (63.89%)	
n (%) prior chemotherapy	85 (32.08%)	72 (33.49%)	0.743
Mean time interval (SD) between end of chemotherapy/start of radiotherapy, days	27.05 (11.44)	26.82 (13.55)	0.937

[a] Number of patients receiving radiotherapy with a 4 MV or 6 MV linear accelerator.
[b] Measured by breast diameter (calculated as the distance between the two entrance points of the beams).

Statistical analysis

Patients' characteristics between groups were compared using Student *t*-test (for continuous variables), chi-square tests (for categorical variables), or two-sample proportion test (for percentages).

The incidence of MD was analysed using proportion tests and a logistic regression with treatment group (hydroactive vs dexpanthenol), breast size (small vs large, with a diameter of 20 cm arbitrarily chosen as cut-off), and prior chemotherapy (whether patients had chemotherapy before radiotherapy or not) as predictor variables.

Time to onset of MD was analysed by means of Cox proportional hazard regression using the same predictors. Kaplan–Meier method was used to estimate MD-free survival (i.e., time before developing MD) and survival curves between treatment groups were compared using log-rank tests. As time to onset was expressed in received cumulative radiation dose, patients who did not develop MD during therapy were assigned the censored value of 66 Gy (25 × 2Gy + 8 × 2 Gy). Five patients (three in the dexpanthenol group and two in the hydroactive group) developed MD during boost irradiation but the precise date of onset was missing. They were then attributed values censored at the fraction corresponding to the last observation made (e.g., if the last observation before the end of radiotherapy occurred after three boost fractions, and the patient developed MD some – unknown – time thereafter, the patient was attributed a censored value of 56 Gy [25 × 2Gy + 3 × 2 Gy]).

All statistical analyses were performed using SAS® 9.2 (SAS Institute Inc., Cary, NC). Unless otherwise specified, significance

[1] This period was chosen as it corresponds to the period generally associated with the onset of skin reactions (i.e., 2–3 weeks, see for example Paterson et al., 2012, for a similar time period). However, in order to verify that this decision could not have affected our results, all statistical analyses were performed again in two separate sets with, in the hydroactive group: 1) all patients who used the hydroactive colloid gel ($N = 236$) and 2), only those patients who applied the hydroactive colloid gel from day 13 as intended ($N = 185$). All these additional analyses led to the same findings as the ones presented in the Results section and are therefore not reported here.

tests were conducted assuming the conventional significance level of 5% ($p < 0.05$, two-tailed).

Results

Patients characteristics

Characteristics of the two patients groups are presented in Table 1. There were no significant differences between the groups with respect to age, radiation energy level received, breast size, the number of patients who had received chemotherapy prior to radiotherapy, and, for those who had, mean time between the end of chemotherapy and the start of radiotherapy.

Incidence of moist desquamation

The results of the logistic regression (summarized in the upper part of Table 2) indicated that the effects of group and of breast size were significant (with odds-ratios of 0.35 and 4.05, resp.). Whether patients had chemotherapy before radiotherapy or not did not significantly affect the incidence of MD. There were no significant interactions between these three variables ($ps > 0.06$).

Overall, MD was significantly more frequent in patients in the dexpanthenol than in the hydroactive group (31.84% vs 16.20%, resp., $Z = 3.95$, $p < 0.0001$) and in patients with large than with small breasts (33.33% vs 12.31%, resp., $Z = 5.25$, $p < 0.0001$).

As breast size is associated with an increased risk of developing MD (e.g., Glean et al., 2001), we dichotomized all patients according to their breast size (i.e., small vs large, with a diameter of 20 cm as cut-off) and examined, within each subgroup, the influence of the treatment on the incidence of MD. In the subgroup of patients with small breasts (i.e., diameter < 20 cm), the incidence of MD was higher in the dexpanthenol than in the hydroactive group but this difference did not reach statistical significance (15.38% vs 7.69%, resp., $Z = 1.60$, $p = 0.055$). However, for patients with large breasts (i.e., diameter ≥ 20 cm), the difference in favour of the hydroactive colloid gel was significant (44.67% vs 21.01% for the dexpanthenol and the hydroactive group, resp., $Z = 4.25$, $p < 0.0001$).

So, large-breasted women were at higher risk of developing radiotherapy-induced MD. More importantly, the incidence of MD was significantly lower (by half) in the hydroactive than in the dexpanthenol group, particularly in patients with large breasts.

Time to onset of moist desquamation

Cox's regression showed that, as for the incidence of MD, only treatment group and breast size significantly affected time to onset of MD (see the lower part of Table 2): MD developed significantly later in the hydroactive than in the dexpanthenol group (Hazard Ratio [HR] = 0.39) and in patients with small than with large breasts (HR = 3.66).

Fig. 1A shows the Kaplan–Meier curves for time until MD onset for the two treatment groups. In both groups, MD begins to develop after a cumulative radiation dose of 26 Gy. The two survival curves are parallel (and remain very close to each other) until the cumulative radiation dose of 40 Gy, at which point they begin to diverge, with patients in the hydroactive group demonstrating greater MD-free survival (log-rank $p < 0.0001$).

As for the analyses of incidence rates, we separately compared time to onset of MD between the dexpanthenol and the hydroactive group within subgroups of patients with small and with large breasts (see Fig. 1B). The effect of treatment was significant in both subgroups (stratified log-rank $p = 0.037$ in the subgroup of patients with small breasts and $p < 0.0001$ in the subgroup of patients with large breasts).

So, regardless of breast size, patients in the hydroactive group developed MD significantly later than patients in the dexpanthenol group.

Table 2
Regression analyses on the incidence and time to onset of moist desquamation (MD).

Variable	Wald Chi-square	Odds ratio	95% CI[a]	*p*
Logistic Regression on the Incidence of MD				
Treatment group[b]	19.46	0.35	0.22–0.56	<0.0001
Breast size[c]	20.40	4.05	2.44–6.71	<0.0001
Prior chemo[d]	0.04	1.05	0.66–1.67	0.831
Variable	**Chi-square**	**Hazard ratio**	**95% CI**	***p***
Cox's Proportional Hazards Regression on Time to Onset of MD				
Treatment group[b]	20.67	0.39	0.26–0.58	<0.0001
Breast size[c]	28.65	3.66	2.28–5.89	<0.0001
Prior chemo[d]	0.07	1.05	0.72–1.55	0.787

[a] *CI*: Confidence interval.
[b] *Treatment group*: Hydroactive group vs Dexpanthenol group.
[c] *Breast size*: dichotomized in small vs large breasts (i.e., diameter $<$ vs ≥ 20 cm, resp.).
[d] *Prior chemo*: whether patients had chemotherapy before radiotherapy or not.

Discussion

The results of this retrospective study revealed that using a hydroactive colloid gel (as compared to a dexpanthenol-containing cream) decreased (by half) the risk of developing radiotherapy-induced moist desquamation in breast cancer patients.

The main reason to compare these two topical agents was that both were routinely used in our radiotherapy department as part of our skin care protocol. For many years, dexpanthenol was used in our department as a prophylactic agent for radiodermatitis. Later on, a new formulation combining absorbing and moisture-donating properties, a hydroactive colloid gel, was added to our skin care protocol and replaced dexpanthenol to manage acute skin reactions. The present retrospective study aimed at comparing these two products, illustrating the need for departments to evaluate (and possibly update) their clinical practices in order to apply evidence-based practice instead of practices based on local preferences and clinical experience.

Although dexpanthenol has shown beneficial effects in various skin disorders (Ebner et al., 2002), evidence supporting its effectiveness in preventing radiotherapy-induced skin reactions remains insufficient (Wong et al., 2013). On the other hand, while hydroactive colloid gels are considered ideal for the management of minor cutaneous wounds (Ferreira Alves et al., 2009; Korting et al., 2011), they have not been exploited much to date and scientific evidence regarding their effectiveness is scarce, particularly for the management of radiation dermatitis. Only one study reported beneficial effects of such a hydroactive colloid gel on the incidence of severe radiotherapy-induced skin reactions and on healing rates (Huang et al., 2005). In their study, the reported incidence of severe skin reactions was somewhat lower that the one we found in our study (10% vs 16%, resp.) but this can be attributable to several differences such as study population and sample size (60 patients with head and neck cancer vs 483 breast cancer patients in our study) or more importantly, endpoints (RTOG grade $\geq$3 vs WHO grade 3, resp.). Nevertheless, the present study confirms the efficacy of a hydroactive colloid gel in preventing MD. To our knowledge, this is the first large-scale study on the use of this type of topical agent for the management of radiation dermatitis.

The present study is not without limitations, mainly related to its retrospective design. For instance, a number of variables pertaining to intrinsic risk factors could not be taken into consideration (e.g., skin type, smoking status). Also, data about follow-up

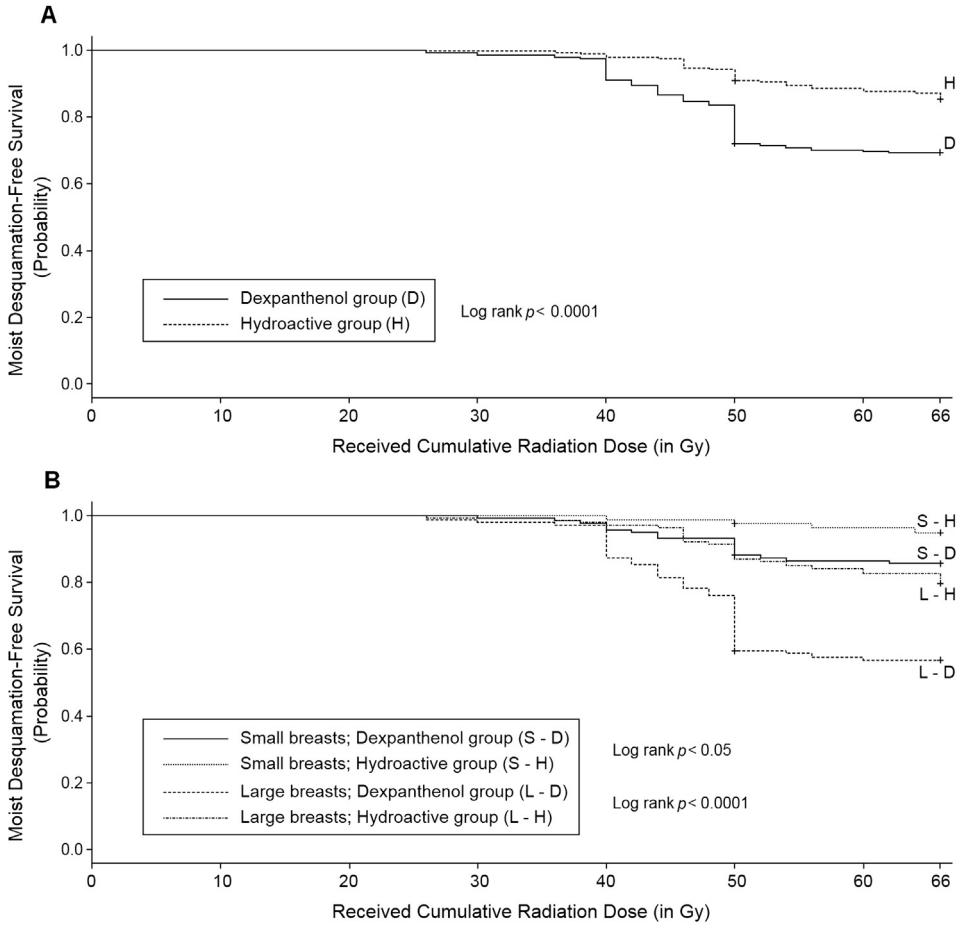

Fig. 1. Kaplan–Meier estimates of moist desquamation-free survival for (A) the two treatment groups (hydroactive vs dexpanthenol) and (B) the two treatment groups within subgroups of patients dichotomized according to their breast size (small vs large breasts).

evaluation of skin reactions were not available, so that analyses on healing time could not be conducted. Finally, there were no measures pertaining to patients' experience (e.g., subjective skin assessment, evaluation of pain, itching, or quality of life), so that the clinical significance of our findings could not be assessed from the patients' point of view.

It should also be mentioned that, due to its retrospective design, the present study compared not only two different agents but also two different vehicles (i.e., an oil-in-water emulsion vs a gel). These vehicles mostly differ with respect to the proportion of water, oil, and alcohol they contain, and with respect to the presence (or absence) and type of emulsifying agents. Unfortunately, for both products used in the present study, the precise concentration of each ingredient was not mentioned by the manufacturers. As vehicles can affect skin hydration, its barrier function, and the percutaneous absorption of active compounds, which can significantly influence wound healing (e.g., Franklin and Franz, 2006; Wiedersberg et al., 2009; Zhai and Maibach, 2001), we cannot rule out the possibility that this difference in vehicles may also have played a role in our findings (above the role of the active ingredients). Therefore, future studies should include vehicle controls in order to eliminate this confounding factor.

The main strengths of the present study included the large sample size and the homogeneous population that minimized the influence of treatment-related risk factors (all patients having undergone breast-sparing surgery, received the same irradiation fractionation regime, and followed the same skin care protocol except for the two topical agents under study).

In conclusion, the present study demonstrated a clear clinical benefit of a hydroactive colloid gel over an oil-in-water emulsion containing 5% dexpanthenol for the prevention of radiotherapy-induced moist desquamation: Its incidence was significantly lower, and time to onset significantly delayed, in patients who applied the dexpanthenol cream then, from day 11–14 of radiotherapy, the hydroactive colloid gel, compared with patients applying the dexpanthenol cream throughout the radiotherapy. Further research, preferably using prospective, vehicle-controlled designs, is warranted to better investigate the efficacy of hydroactive colloid gels in the prevention and management of radiotherapy-induced skin reactions. In our department, a prospective study is currently under way to investigate whether the use of this hydroactive colloid gel from the start of the radiation therapy will further improve the prevention of moist desquamation following radiotherapy for breast cancer.

Conflict of interest statement

None declared.

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Efficacy of a hydroactive colloid gel versus historical controls for the prevention of radiotherapy-induced moist desquamation in breast cancer patients

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ABSTRACT

Purpose: Radiotherapy-induced moist desquamation (RIMD) is a complication that can affect patients' quality of life and jeopardize radiotherapy outcomes. The curative use of a hydroactive colloid gel has previously been shown effective in the management of RIMD in breast cancer patients. This study aimed at investigating the efficacy of this same gel but in the *prevention* of RIMD.
Methods: A group of breast cancer patients who applied the hydroactive gel from start to end of post-lumpectomy radiotherapy (Preventive Hydrogel group) were compared with two groups of matched historical controls: a group applying a dexpanthenol cream throughout their therapy and a group applying first the dexpanthenol cream then, after 11–14 fractions of radiotherapy, the hydroactive gel (Curative Hydrogel group). All patients received identical fractionation regimen. The clinical outcomes were the incidence and time to onset of RIMD.
Key results: After 25 fractions of radiotherapy (50 Gy), patients in the Preventive Hydrogel group (N = 202) developed RIMD significantly less frequently and later than patients in the Dexpanthenol group (N = 131; incidence = 7% vs 35% respectively, odds ratios = 7.27; probability of RIMD-free survival after 50 Gy = 0.88 vs 0.62). There were no significant differences between the Preventive and the Curative Hydrogel group (N = 87).
Conclusions: These findings confirm our previous results: applying the hydroactive colloid gel, rather than dexpanthenol, delayed the onset and reduced the incidence of RIMD in breast cancer patients. However, applying the hydrogel preventively offered no statistically significant advantages over applying it curatively.

1. Introduction

About 70–80% of breast cancer patients will undergo radiation therapy at some point as part of their cancer treatment (Barton et al., 2014). Of these, up to 90–95% will develop, to some extent, skin reactions during or shortly after the completion of radiotherapy (Sundaresan et al., 2015; The FAST Trialists group, 2011). Acute skin reactions, or radiation dermatitis, occur as a consequence of ionizing radiation, as used in radiotherapy, that damages the mitosis of skin cells (hampering their regeneration and thereby, damaging the integrity of the upper layer of the skin) and alters the healing process (leading to structural, histologic, and vasculature changes of the skin and underlying connective tissue). Ultimately, irradiation leads to inflammation, decreased functional stem cells, altered endothelial cells, and cell apoptosis and necrosis. Moreover, irradiation has a cumulative effect on the skin, so that skin reactions aggravate during the course of radiotherapy (Denham and Hauer-Jensen, 2002; Gieringer et al., 2011). The risk of developing radiation dermatitis and its severity depend on multiple factors,

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including the location of the irradiated zone, with body regions containing skin folds (such as the groin or the breasts) being at higher risk. The total irradiation dose and the fractionation regimen (i.e., the dose delivered per fraction), the volume of tissue that is irradiated, the use of other concurrent cancer therapies (e.g., concomitant chemotherapy increases the risk, Fiets et al., 2003), or larger breast size constitute other risk factors for radiation dermatitis (e.g., Fowble et al., 2016; Hymes et al., 2006; Kraus-Tiefenbacher et al., 2012).

The severity of radiation dermatitis is graded on a continuum ranging from dryness or red rashes and dry desquamation to the more severe moist desquamation (O'Donovan et al., 2015). Radiotherapy-induced moist desquamation (RIMD), characterised by sloughing skin blisters filled with serous exudate, typically occurs after four to five weeks of radiotherapy (after a cumulative radiation dose of 40 Gray [Gy]), peaks shortly after the end of therapy, and heals within three months after completion of therapy (Hymes et al., 2006). Despite this gradual (natural) healing and its relatively low incidence (10–15%, Wells and MacBride, 2003), RIMD can be particularly painful and distressing for patients, potentially necessitating an interruption of radiation treatment (Kirova et al., 2011; Pommier et al., 2004) and in rare cases resulting in local infection (Salvo et al., 2010), all of which can negatively influence treatment outcome (Bese et al., 2007).

Over the years a large variety of products have been used to prevent and manage RIMD (e.g., calendula, gentian violet, hyaluronic acid, lanolin gauze dressings, sulfadiazine, or silicone dressings, see for example D'Haese et al., 2005; Harris et al., 2012; O'Donovan et al., 2015; Yuen and Arron, 2016). Yet there is insufficient (and even conflicting) evidence as to the efficacy of these products and many reviews and meta-analyses highlight the lack of strong, consistent scientific evidence regarding which product to use or when to use it for optimal results (Feight et al., 2011; The Society and College of Radiographers, 2015; Wong et al., 2013).

In a previous study (Censabella et al., 2014), we retrospectively compared the efficacy of a 5% dexpanthenol cream with a hydroactive colloid gel that combines the moisturising and absorbing properties of hydrocolloids and hydrogels. Dexpanthenol, one of the agents commonly used in radiotherapy centres (O'Donovan et al., 2015), is an alcohol analogue of pantothenic acid, a provitamin known to accelerate and improve wound healing by promoting epithelial formation and regeneration. It acts like a moisturizer when used topically and reduces itching and inflammation (Ebner et al., 2002), though evidence supporting its effectiveness in preventing radiotherapy-induced skin reactions remains insufficient (Wong et al., 2013). The hydroactive colloid gel contains purified water, arginine (an amino acid essential for cell division), branched-chain fatty acid, and a polymer in an active and an inactive state. The action of this polymer is determined by the wound itself: in dry wounds, the active polymer donates moisture ("hydrogel" effect) and, in exuding wounds, the inactive polymer is activated by the exudate and then absorbs it ("hydrocolloid" effect), maintaining an optimal moist environment that improves wound healing (Field and Kerstein, 1994). We found a significantly lower incidence and a delayed time to onset of RIMD in breast cancer patients who applied the dexpanthenol cream then, after 11–14 days, replaced it with the hydroactive colloid gel, than in those patients applying the dexpanthenol cream throughout the radiotherapy (16% vs 32%). Further, RIMD occurred significantly later with the hydroactive colloid gel than with the dexpanthenol cream.

The aim of the present study was to investigate the efficacy of this same hydroactive colloid gel in the *prevention* of RIMD, with the hypothesis that using this agent preventively would be even more beneficial with respect to incidence and onset time of RIMD. Therefore, we asked a group of breast cancer patients to apply this hydroactive colloid gel throughout their radiotherapy and compared them with these two previous groups of patients serving as historical controls.

2. Methods

2.1. Participants

All women who underwent conservative surgery for breast cancer and were further scheduled for conventional radiotherapy at the Limburg Oncologic Centre (Hasselt, Belgium) between June 2012 and July 2013 were screened for eligibility. Patients were included if they were to receive 25 daily fractions of 2 Gy to the whole breast (five times/week) followed by an 8-fraction boost to the tumour bed, for a total dose of 66 Gy. Exclusion criteria were previous irradiation to the same breast, metastatic disease, use of bolus material, and concomitant chemotherapy (adjuvant or neo-adjuvant chemotherapy, hormone therapy and/or trastuzumab was allowed). The study protocol was approved by the local Medical Ethics Committee.

A group of 222 patients met these criteria and were included after signed informed consent was obtained. They were required to apply the hydroactive colloid gel (Flamigel®, Flen Pharma NV, Kontich, Belgium) to the irradiated area from start to end of radiotherapy (hereafter referred to as the Preventive Hydrogel group). This group was compared with two groups of matched historical controls from the previous study (Censabella et al., 2014), enrolled with the same eligibility criteria, hence undergoing the same radiotherapy regimen post-lumpectomy: the first group applied a 5% dexpanthenol cream (Bepanthol® Cream, Bayer AG, Leverkusen, Germany) throughout their radiotherapy (Dexpanthenol group, N = 136), the second one applied the dexpanthenol cream from the start of radiation therapy then, after 11–14 days, replaced it with the hydroactive colloid gel until completion of therapy (Curative Hydrogel group, N = 100). To note, originally, the two historical control groups had equivalent sample size but half of these patients received the first 25 fractions with 4-MV photons beams (they were only 20% in the Preventive Hydrogel group). As this was a somewhat outdated technique and a potential bias we decided to exclude these patients, what led to this rather unbalanced design.

2.2. Radiation therapy and skin care

Radiotherapy was planned using the Eclipse™ treatment planning system (version 10.0, Varian Medical System, Palo Alto, CA) and treatment was delivered by 6 MV photon beams. Segmented fields were used where required in order to reduce hot spots. The second series of boost was delivered using either photon (6–18 MV) or electron beams (9–15 MeV).

During radiotherapy, skin care protocol remained the same for all three groups. Patients were asked to follow general skin care recommendations (e.g., gently washing with mild soap or non-soap cleansers; patting dry with a soft towel instead of rubbing; wearing soft, loose clothing) and were instructed to apply a dollop of product three times a day. Dry/patchy moist desquamation was treated by applying a self-adhesive silicone foam as secondary dressing (Mepilex® or Mepilex Lite®, Mölnlycke Health Care, Gothenburg, Sweden). In case of confluent moist desquamation, patients stopped using either the dexpanthenol cream or the hydroactive colloid gel and other wound care products more appropriate to moderately to heavily exuding wounds were applied.

2.3. Endpoints

As in the previous study, radiation oncology nurses recorded the date of onset of RIMD irrespective of its severity (i.e., as the first sign appeared). Since the nurses used the World Health Organization criteria for grading acute cutaneous toxicities (0: no changes, 1: erythema, 2: dry desquamation, 3: moist desquamation, 4: necrosis; World Health Organization, 1979), no additional information on the severity of RIMD was available. Also, for each participant, breast size was taken into account, measured by tangential field separation (breast width, in cm, calculated at the posterior border of the medial and lateral tangential beams). Also, we recorded whether chemotherapy had been administered prior to radiotherapy (and, if so, the time interval between the end of chemotherapy and the start of radiotherapy). No other information on patient-related risk factors (such as smoking status or body mass index) or patient-reported outcomes (such as pain or itching) was collected as these pieces of information were unavailable for patients of the control groups.

2.4. Statistical analysis

Patients' characteristics between groups were compared using one-way analyses of variance (ANOVAs, for continuous variables, with Bonferroni adjustments for paired comparisons), or chi-square tests (for categorical variables, using two-sample proportion tests for percentages).

The incidence of RIMD was analysed using chi-square tests and two-sample proportion tests. We also performed univariate and multivariate logistic regressions with, as predictor variables, age, group (with the Preventive Hydrogel group as reference group), whether patients had prior chemotherapy or not, and breast size (i.e., tangential field separation).

Time to onset of RIMD (as a function of received cumulative radiation dose, in Gy) was analysed by means of univariate and multivariate Cox proportional hazard regressions using the same predictors. Kaplan-Meier method was used to estimate RIMD-free survival (i.e., time before developing RIMD, expressed as received cumulative radiation dose, in Gy). As breast size is associated with an increased risk of developing radiation dermatitis (e.g., Fowble et al., 2016; Wells and MacBride, 2003), we categorised the patients according to their breast size (based on their field separation) and used this variable as strata. (To prevent over-representation of one category, we used the 35th and 65th percentiles computed on the whole dataset; small breasts < pc 35, large > pc 65).

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) software version 22.0 (SPSS Inc., Chicago, IL) assuming the conventional significance level of 5% ($p < 0.05$, two-tailed).

3. Results

3.1. Patients' characteristics

Patients' characteristics are presented in Table 1. There were no significant differences between groups with respect to age, prior chemotherapy, breast size, and the use of other skin care products during radiotherapy. However, the three groups significantly differed from each other with respect to the type of boost delivered, with much more patients in both historical control groups having received electron beams. Since electron beams are associated with greater skin toxicity (Johns and Cunningham, 1983; Kempa, 2016; Podgoršak, 2005), we decided, for further statistical analyses, to censor our data at 50 Gy, considering only the patients who developed RIMD before the boost. This led to a final sample size of 420 patients (with 202, 131, and 87 patients in the Preventive Hydrogel, Dexpanthenol and Curative Hydrogel groups, respectively). Note that the pattern of results pertaining to age, prior chemotherapy, breast size, and the use of other skin care products during radiotherapy remained unchanged (non-significant).

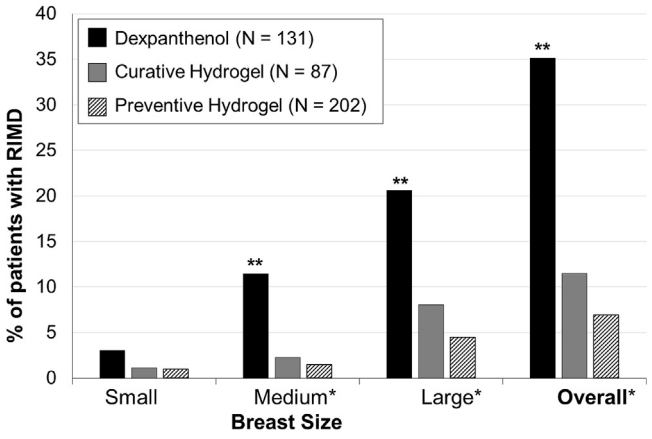
3.2. Incidence of radiotherapy-induced moist desquamation

During the first 25 fractions of radiotherapy (i.e., with data censored at 50 Gy), the incidence of RIMD was overall lower in the Preventive than in the Dexpanthenol and the Curative Hydrogel group (6.9% vs 35.1% and 12.6% [95% CIs: 4.2–11.3%, 27.5–43.6%, and 7.2–21.2%, respectively], $p < 0.0001$, see Fig. 1), though paired comparisons showed that the difference between the two hydrogel groups was not significant ($p = 0.197$). The incidence of RIMD was also the lowest in the Preventive Hydrogel group when considering separately patients according to their breast size (based on the tangential field separation), but only the differences with the Dexpanthenol group for patients with medium and large breasts

Table 1
Patients characteristics.

	Preventive Hydrogel	Dexpanthenol	Curative Hydrogel	p[a]
Characteristics				
N	222	136	100	
Mean age (SD), years	56.50 (10.4)	56.94 (11)	57.94 (10.6)	0.570
Median breast size (SD), cm[b]	21.15 (2.8)	21.45 (3.2)	21.85 (3)	0.174
Breast size, n (%)[b]				0.113
Small (<pc. 35)	81 (36.5%)	43 (31.6%)	23 (23%)	
Medium (pc 35–65)	70 (31.5%)	40 (29.4%)	32 (32%)	
Large (>pc 65)	71 (32%)	53 (39%)	45 (45%)	
Prior chemo, n (%)	86 (38.7%)	45 (33.1%)	36 (36%)	0.556
Mean time interval (SD) end chemo/start RT, days[c]	32.22 (22.9)	31.91 (12.2)	31.7 (15.9)	0.99
Use of other products during skin care, n (%)[d]	160 (72.1%)	99 (72.8%)	69 (69%)	0.798
Type of boost, n (%)[e]				<0.0001
Photon	87 (39.4%)	12 (8.8%)	29 (29.3%)	
Electron	134 (60.6%)	124 (91.2%)	70 (70.7%)	

Abbreviations: SD = standard deviation; pc = percentile; chemo = chemotherapy; RT = radiotherapy.
[a] Chi-square tests or one-way analysis of variance, as appropriate (two-tailed).
[b] Breast size was measured by tangential field separation (breast width, in cm, at the posterior border of the medial and lateral tangential beams).
[c] For those who had chemotherapy prior to radiation therapy, time interval between the end of chemotherapy and the start of radiotherapy.
[d] Patients that received other products (e.g., self-adhesive silicone foam) as skin care at some point during radiotherapy.
[e] Data was missing for one patient of the Preventive Hydrogel and one patient of the Curative Hydrogel group.



* Significant overall difference (chi-square , two-tailed).
** Significant difference with the Preventive Hydrogel group (two-sample proportion tests, two-tailed).

Fig. 1. Incidence of Radiotherapy-Induced Moist Desquamation (RIMD) after 25 fractions (50 Gy) per group and per subgroups of patients with small, medium, and large breast size.

were significant (see Fig. 1). As in our previous study, with the exception of small-breasted patients, the incidence of RIMD was also significantly lower in the Curative Hydrogel group than in the Dexpanthenol group ($p = 0.484$ for patients with small breasts and p's < 0.0001 for patients with medium and large breasts and overall).

Consistent with the literature, RIMD was globally more frequent in patients with medium and large breasts than with small breasts (15% and 28.7% versus 5.1%, $p < 0.0001$, Odds-Ratio [OR] = 3.29 and 7.46 for medium and large breast, 95% CI [OR]: 1.34–8.06% and 3.23–17.27%, respectively). Finally, patients who had had chemotherapy before radiotherapy did not develop RIMD more frequently than patients who had not (17.1% versus 15.9%, respectively, $p = 0.75$, OR = 0.92, 95% CI [OR]: 0.53–1.57%).

Results of the univariate and multivariate analyses conducted on the incidence of RIMD that occurred before the boost are summarized in the upper part of Table 2. In the multivariate analysis (as in the univariate ones), the factors found significantly associated with increased RIMD were group and breast size (Wald $\chi^2(2) = 40.78$ and 28.05, respectively, p's < 0.0001): Patients in the Dexpanthenol and in the Curative Hydrogel group were respectively 7.97 and 1.46 times more likely to develop RIMD than patients in the Preventive Hydrogel group, but this latest difference was not statistically significant ($p = 0.401$). Bear in mind that, as the data was censored at 50 Gy (i.e., before the boost), the type of boost (electron vs photon) was not entered into the analysis.

3.3. Time to onset of radiotherapy-induced moist desquamation

Univariate and multivariate Cox's regression performed on censored data (i.e., on RIMD that occurred before the boost, with patients who did not develop RIMD being assigned the censored value of 50 Gy) are outlined in the lower part of Table 2. The multivariate analysis revealed that group and breast size (Wald $\chi^2(2) = 41.62$ and 33.38, p's < 0.0001) significantly affected time to onset of moist desquamation. RIMD developed later in the group applying the hydroactive gel preventively than in the Dexpanthenol (Hazard Ratio [HR] = 5.95) or the Curative Hydrogel group (HR = 1.48) but again, this latter difference was not significant.

The Kaplan-Meier curves for time to onset of RIMD for the three groups, depicted in Fig. 2, showed that patients in the Preventive Hydrogel group had the greatest probability of RIMD-free survival. RIMD developed first in the Dexpanthenol group after a cumulative radiation dose of 26 Gy, whereafter the probability of RIMD-free survival rapidly and strongly decreased. In the two hydrogel groups, RIMD developed after a cumulative radiation dose of 38 and 32 Gy (for the Curative and Preventive group, respectively) and slowly decreased, the two survival curves closely overlapping. After 25 fractions of radiotherapy, the probability of RIMD-free survival was 93%, 88%, and 65% for the Preventive Hydrogel, Curative Hydrogel, and Dexpanthenol, respectively (log rank $p < 0.0001$). Pairwise comparisons showed that the Preventive Hydrogel group significantly differed from the Dexpanthenol group but not from the Curative Hydrogel group (log rank $p < 0.0001$ and $= 0.206$, respectively).

We also conducted Kaplan-Meier with breast size as strata and found significant differences between the survival curves in patient with medium and large breasts only (see Fig. 3). Pairwise comparisons per breast size revealed that the Preventive Hydrogel was significantly different from the Dexpanthenol group but not from the Curative Hydrogel group (in the medium and large breast size subgroup: log rank $p = 0.001$ and < 0.0001 for the comparison with Dexpanthenol, and $= 0.620$ and 0.537 for the comparison with the Curative Hydrogel group, respectively). Note that the two historical control groups also differed from each other for patients with medium and large breasts (log rank $p = 0.005$ and < 0.0001, respectively).

Table 2
Univariate and multivariate regression analyses on the incidence and time to onset of Radiotherapy-Induced Moist Desquamation (RIMD, data censored at 50Gy).

Factor	Univariate analyses			Multivariate analyses		
	OR/HR	95% CI	p	OR/HR	95% CI	p
Logistic regression						
Dexpanthenol vs Preventive Hydrogel	7.27	3.79–13.93	<0.0001	7.97	3.98–15.94	<0.0001
Curative vs Preventive Hydrogel	1.74	0.74–4.1	0.202	1.46	0.60–3.56	0.401
Age	1.02	0.99–1.04	0.154	1.01	0.98–1.04	0.596
Prior Chemo[a]	0.92	0.53–1.57	0.750	0.97	0.51–1.83	0.924
Breast Size (continuous)[b]	1.28	1.17–1.41	<0.0001	1.31	1.18–1.44	<0.0001
Cox's Proportional Hazards Regression						
Dexpanthenol vs Preventive Hydrogel	5.88	3.23–10.71	<0.0001	5.95	3.26–10.86	<0.0001
Curative vs Preventive Hydrogel	1.67	0.74–3.76	0.215	1.48	0.66–3.34	0.341
Age	1.01	0.99–1.04	0.176	1.01	0.98–1.03	0.557
Prior Chemo[a]	0.91	0.56–1.49	0.713	1.04	0.62–1.75	0.876
Breast Size (continuous)[b]	1.22	1.14–1.30	<0.0001	1.22	1.14–1.31	<0.0001

Abbreviations: OR = odds ratio; HR = hazard ratio; CI = Confidence Intervals.
[a] *Prior Chemo*: whether patients had chemotherapy before radiotherapy or not.
[b] *Breast Size:* tangential field separation (breast width, in cm, at the posterior border of the medial and lateral tangential beams).

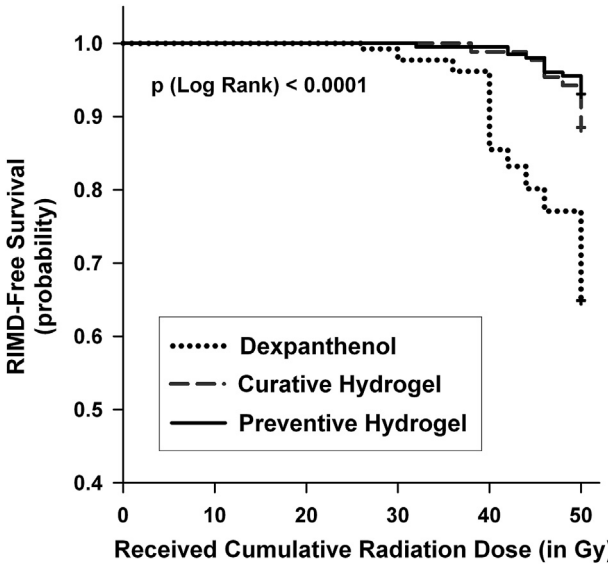


Fig. 2. Kaplan-Meier estimates of Radiotherapy-Induced Moist Desquamation (RIMD)-free survival (at 50 Gy) for the three groups.

4. Discussion

The results of this study showed that, overall, the incidence of RIMD was significantly the lowest in the Preventive Hydrogel group, though the difference between the preventive and the curative use of the hydroactive colloid gel was not statistically significant. Moreover, patients in the Preventive Hydrogel group developed RIMD significantly later than patients in the Dexpanthenol group (but not than patients in the Curative Hydrogel group), with greater RIMD-free survival probability. When taking breast size into account, these differences in incidence and time to onset remained statistically significant for patients with medium and large breast size. For small-breasted patients, however, the three groups did not significantly differ from each other.

In a previous study, we retrospectively compared the two groups used here as controls (Dexpanthenol vs Curative Hydrogel groups) and found a clear clinical benefit of the hydroactive colloid gel for the management of RIMD (Censabella et al., 2014). The present results confirm these previous findings: Applying the hydroactive colloid gel from the start of radiotherapy rather than dexpanthenol led to both a delayed onset and reduced incidence of RIMD.

Hydroactive colloid gels, that combine the moisturising and absorbing properties of hydrocolloids and hydrogels, enable the interaction with the wound bed to maintain an optimal moist environment, following the state-of-the-art principle of moist wound healing (Field and Kerstein, 1994; Morton and Phillips, 2012). Therefore, they are considered ideal for the management of minor, lightly to moderately exuding wounds (Ferreira Alves et al., 2009; Korting et al., 2011), hence, particularly suitable for radiation dermatitis (Glean et al., 2001). However, to date, evidence supporting the use of hydroactive colloid gels for preventing and managing radiation dermatitis is scarce and inconsistent (Wong et al., 2013). For instance, in a randomized study comparing a hydrogel dressing to gentian violet, Mak et al. (2000) found no group differences in healing times but decreased wound size and pain in the gentian violet group, although this latter product was rated by the patients as being less comfortable. In a similar study, Macmillan et al. (2007) randomly allocated patients who developed RIMD to a hydrogel vs dry dressing and observed no group

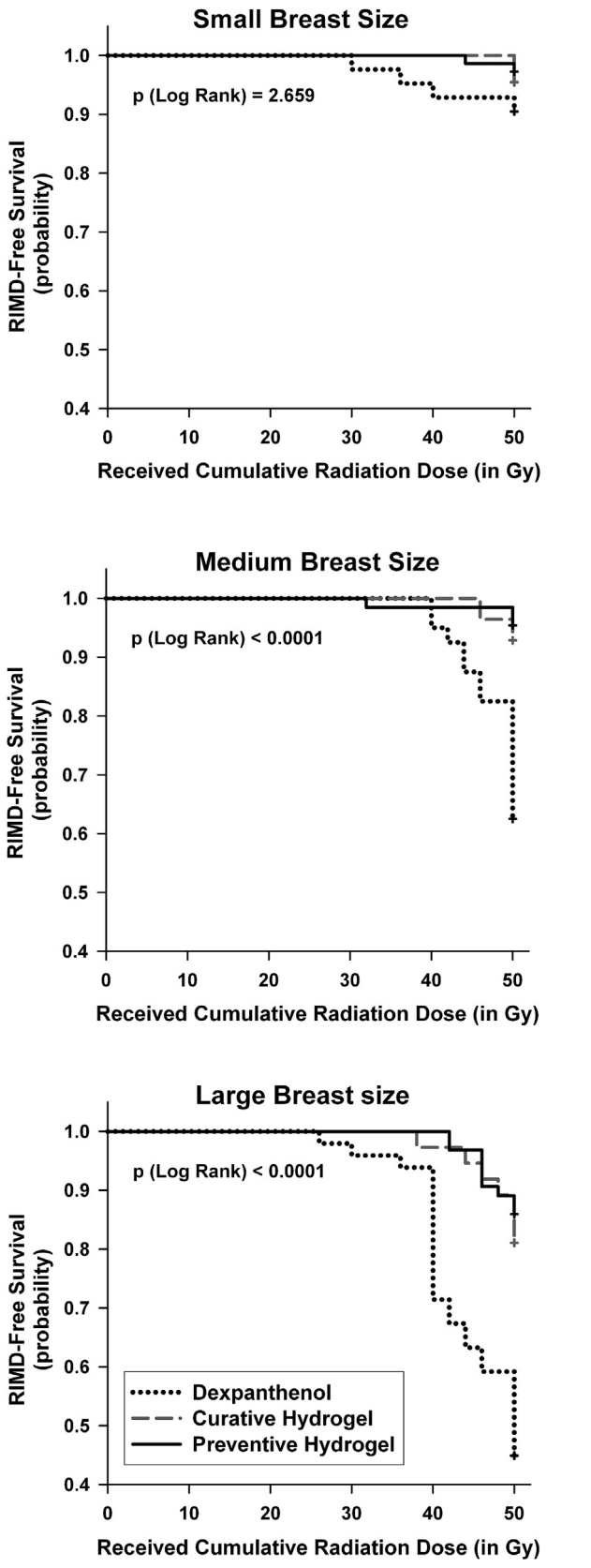


Fig. 3. Kaplan-Meier estimates of Radiotherapy-Induced Moist Desquamation (RIMD)-free survival (at 50 Gy), per group, for subgroups of patients with small, medium, and large breast size.

difference in pain or itching but prolonged healing time in patients applying the hydrogel. In contrast, when comparing hydrogel dressing with gentian violet, Gollins et al. (2008) found shorter healing times in patients applying the hydrogel. Likewise, in a small randomized controlled trial, Huang et al. (2005) found a lower incidence of severe skin reactions and higher healing rates in patients applying the same hydroactive colloid gel as the one we used in the present study compared to their routine clinical skin care practice.

Actually, in their latest clinical guidelines, the Skin Toxicity Study Group of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) did not find sufficient evidence to support a recommendation for or against dressings in the management of acute radiation dermatitis (Wong et al., 2013). Similarly, in her systematic review on the management of RIMD, Kedge (2009) qualified the evidence in favour of hydrogels and hydrocolloids as mixed (although they seemed beneficial with respect to patient comfort) and concluded that research on such products was urgently needed. Together with our previous study, the present study is an attempt to help fill this gap.

This study was not without limitations, mainly due to its design. Indeed, the use of historical controls precluded the collection of any additional data such as follow-up data (e.g., healing time), data on patient-related risk factors (e.g., smoking, body mass index, or co-existing chronic illnesses; see for example Hogle, 2010; Kraus-Tiefenbacher et al., 2012; Macmillan et al., 2007; Sharp et al., 2013; Wells et al., 2004; Yom et al., 2016), and data on patient-reported outcomes (e.g., quality of life measures or subjective assessment of symptoms such as pain or itching), thereby preventing more fine-tuned analyses.

Finally, the products under study not only differed in ingredients (i.e., dexpanthenol vs acid colloidal hydrocolloid) but also in vehicles (i.e., oil-in-water emulsion vs gel). Vehicles can affect skin hydration, its barrier function, and the percutaneous absorption of active compounds, which can significantly influence wound healing (e.g., Franklin and Franz, 2006; Wiedersberg et al., 2009; Zhai and Maibach, 2001). Therefore, we cannot rule out the possibility that this difference in vehicles may also have played a role in our findings (above the role of the agent itself).

The main strengths of this study were the large number of patients and their homogeneity across all groups (all patients having undergone breast-sparing surgery, received the same irradiation fractionation regimen, and followed the same skin care protocol except for the topical agents under study), so that the influence of treatment-related risk factors could be minimised.

In conclusion, in the present study, we demonstrated that the preventive application of a hydroactive colloid gel throughout radiotherapy in breast cancer patients led to a delayed onset and reduced incidence of RIMD compared to dexpanthenol. Yet applying the hydroactive colloid gel from the start of radiotherapy did not led to statistically significant advantages over applying it after fraction 11 to 14 (i.e., after onset of erythematous radiation dermatitis). It should be acknowledged that, as patients in the Curative Hydrogel group applied the dexpanthenol cream during the first 10 to 13 fractions of radiotherapy, we cannot be sure that the results would remain the same if patients did not apply the dexpanthenol first (though the curative use of the hydroactive colloid gel did offer significant advantages over Dexpanthenol in this study and in the previous one, see Censabella et al., 2014). Nevertheless, from a practical perspective, using a single product during radiotherapy is much more convenient for patients than using two different products as they did in the Curative Hydrogel control group. Moreover, as a (non-sticky) gel, it presents the additional advantage of being easy to use and to remove (with a cooling effect and no discomfort, irritation, or tissue damage commonly associated with dressing changes) and does not necessarily require secondary dressing or additional taping. Such advantages are not negligible because they alleviate patients' discomfort (and possibly pain and irritation), an aspect that also ought to be taken into account in skin care practice (McQuestion, 2011; Wells and MacBride, 2003). Accordingly, we updated our skin care protocol in our radiotherapy department, using from now on the hydroactive colloid gel systematically from start of radiotherapy.

Conflict of interest statement

None.

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A CLINICAL STUDY COMPARING A HYDROACTIVE COLLOID GEL WITH A DEXPANTHENOL CREAM FOR THE **TREATMENT OF SKIN REACTIONS IN BREAST IRRADIATION**

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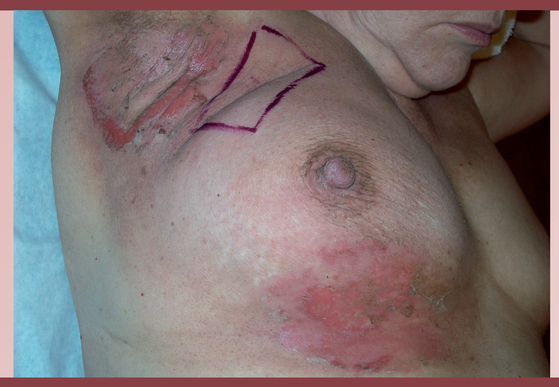
PURPOSE/OBJECTIVES

Dermatitis is a frequent side effect of radiation therapy (see Figure 1). Optimal skin hydration is widely accepted to prevent radiation dermatitis but there is no general consensus on which hydrating agent to use,1 although the use of hydroactive colloid gels has been recommended.2,3 The objective of this retrospective study was to **compare the efficacy of a hydroactive colloid gel** (Flamigel®) **and a dexpanthenol cream** (Bepanthol®) **in preventing the development of radiotherapy-induced moist desquamation**.



MATERIALS/METHODS

Data from two cohorts of patients undergoing radiotherapy for breast cancer at the Limburg Oncology Center was retrospectively analysed. The first cohort (Sept.2009-2010) **applied the dexpanthenol cream throughout their radiation therapy** (3 times a day, every day). The second cohort (Sept. 2010-2011) **applied the dexpanthenol cream during 12 days and replaced it from day 13 by the hydroactive colloid gel** (i.e., after a received cumulative radiation dose of 26 Gy). Radiation treatment (technique, total dose, and equipment) was the same for the two cohorts. Patients were further categorized according to their breast size (i.e., distance between the two entrance points of the beams < or ≥ 20 cm), which is a well-known risk factor for radiation dermatitis.4 The presence of moist desquamation was recorded as the first signs appeared. Two-sample proportion tests were performed to compare the efficacy of the two treatments.

The dexpanthenol group included 292 patients and the hydroactive gel group, 281 patients. There were significantly more patients with large breast size in the hydroactive gel than in the dexpanthenol group (see Table 1). Consistent with the literature, the overall incidence of moist desquamation was significantly greater in patients with large than with small breast size (32% vs 13%, resp., $p < .0001$). Yet, despite this, **the overall incidence of moist desquamation was significantly lower (by almost half) in patients who applied the hydroactive gel than in those who applied the dexpanthenol cream** (see Table 1.). Finally, in patients with small breast size, there was no significant difference between the two treatments on the incidence of moist desquamation. However, **for patients with large breast size, the hydroactive gel significantly decreased the risk of developing moist desquamation** (see Table 1).

Table 1. Number (N) and proportion (%) of patients and incidence of moist desquamation per group and breast size.

	Group dexpanthenol		Group hydroactive gel	
Total N	292		281	
N (%) Small Breast size	121 (41.4%)		93 (33.1%)*	
N (%) Large Breast size	171 (58.6%)		188 (66.9%)*	
N (%) with moist desquamation	**92 (31.50%)**		**49 (17.43%)*** **	
	Small breast size		**Large breast size**	
	Group dexpanthenol (N = 121)	Group hydro-active gel (N = 93)	Group dexpanthenol (N = 171)	Group hydro-active gel (N = 188)
N (%) with moist desquamation	**18 (14.9%)**	**9 (9.7%)**	**74 (43.3%)**	**40 (21.3%)*** **

Note. *Small/ Large breast size = distance between the two entrance points of the beams < or ≥ 20 cm.*
**p < .05, ***p < .0001 (two-sample proportion tests, one-tailed)*

CONCLUSIONS

The use of a hydroactive colloid gel (as compared with a dexpanthenol cream) significantly reduces the risk of radiation dermatitis (by almost half), particularly in patients with larger breast size who are at higher risk of developing moist desquamation.

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·专家论坛·

本文亮点：

该文分别从水凝胶的基质材料、特殊结构、复合特殊功能等方面总结阐述了功能性水凝胶促进创面修复的作用与相关研究进展，突出了水凝胶在创面修复领域中的广泛应用，并且对未来新型水凝胶的研究方向进行了展望，以期实现更高质量的创面修复。

功能性水凝胶促进皮肤创面的修复

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【摘要】 皮肤创面是临床最常见病症之一，如何快速、高质量修复各种皮肤创面仍面临许多挑战。随着材料科学和生物医学的快速发展和交叉融合，水凝胶可通过灵活的结构修饰、联合不同功能成分等，集多种优良性能于一体，并被广泛应用于创面治疗与研究。该文分别从水凝胶的基质材料、特殊结构、复合特殊功能等方面阐述其对创面修复的促进作用。

【关键词】 皮肤；　生物相容性材料；　水凝胶；　创面修复

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Role of functional hydrogel in promoting wound healing

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【Abstract】 Cutaneous wounds are one of the commonest clinical diseases. At present, there are still many challenges in how to repair wounds quickly with high quality. With the rapid development and cross-integration of materials science and biomedicine, hydrogels that can integrate various excellent properties through flexible structural modification and combination of different functional components are widely applied in wound management and research. This paper attempted to summarize the role of hydrogel in promoting wound repair from the respects of matrix materials, special structures, and diverse functions of hydrogel.

【Key words】 Skin；　Biocompatible materials；　Hydrogel；　Wound repair

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皮肤是人体与外界之间首要的机械与生物屏障，其结构完整性和功能等受损会形成不同类型的创面。引起皮肤组织损伤的原因包括烧创伤、内科疾病、医源性损伤等。皮肤创面愈合通常分为止血、炎症、增殖、重塑 4 个连续并可能相互重叠的过程，这些过程受到由多种细胞和生物介质组成的复杂网络精确调控。然而，当创面局部微环境包括失控性炎症反应、感染、细胞功能缺陷、营养不良、细胞衰老和蛋白水解失衡等不利于创面修复时，正常的创面修复过程可能被影响或阻断，导致创面愈合延迟，或发展为慢性创面，进而严重影响患者健康甚至生活质量。

自 1962 年 Winter[1] 提出创面湿性愈合理论后，围绕创面修复微环境的基础、转化和临床研究不断深入和细化。医用创面敷料可覆盖创面作为临时屏障，在隔绝微生物感染、保护组织细胞使其发挥正常功能、协调创面修复与组织再生进程等方面有

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着显著效果，是促进临床创面修复的重要方式[2]。理想的医用创面敷料应具备以下特性：(1)良好的安全性与组织相容性；(2)维持创面合适的湿润环境，有利于气体交换，并对创面渗出物有一定吸收作用；(3)足够的物理和机械强度，能维持结构完整性而避免微生物侵入；(4)适当的微结构和生物化学性质，能促进细胞增殖和迁移；(5)避免对创面造成二次伤害[3-4]。

水凝胶由于具有优良的亲水性、生物相容性和类ECM的三维多孔结构，在创面修复管理中有着独特优势。除了可通过改良聚合物骨架、浓度配比、交联方式等优化水凝胶性能，也可通过水凝胶联合生物活性分子、药物或细胞等构建递送系统，根据不同创面定制局部使用的医用创面敷料[5-6]。经过多学科交叉融合和发展，水凝胶也从单一物理覆盖或单一功能转变为多种功能的复合，在创面修复领域具有广阔的应用前景。本文从水凝胶不同功能的角度出发，对近年来笔者课题组以及国内外应用水凝胶促进创面快速、高质量修复的相关研究进展做一介绍。

1 水凝胶基质材料对创面修复的促进作用

不同的水凝胶基质材料对创面修复过程中各类细胞产生不同的生物学效应，对创面修复进程的影响也并不相同。水凝胶基质材料包括天然高分子聚合物，如壳聚糖、明胶、透明质酸、海藻酸和丝素蛋白等，以及合成高分子聚合物，如聚乙二醇、泊洛沙姆、聚乙烯醇、聚丙烯酰胺、聚乳酸-羟基乙酸共聚物和多肽等，这些亲水聚合物可通过化学或物理交联被构建成不同类型的水凝胶，从而用于促进创面修复[7-8]。这些基质材料本身对创面修复相关的细胞的生物学行为和命运有一定的调节作用，从而影响创面愈合过程。例如，胶原蛋白是维持天然ECM生物学和结构完整性的主要有机成分，可以通过不断动态灵活地重塑来调控细胞行为和组织学功能，是水凝胶合成和临床应用中最广泛的基础材料。外源性胶原蛋白可被内源性胶原酶降解，相较于其他天然聚合物具有更好的生物相容性和低抗原性，但仍可对某些细胞产生生物学效应，如Ⅰ、Ⅱ、Ⅲ型胶原蛋白及其降解产生的多肽可刺激Fb趋化至损伤和炎症部位，从而启动修复程序。有学者将普鲁兰多糖与Ⅰ型胶原蛋白结合，制备普鲁兰-胶原水凝胶，该水凝胶具有更加接近天然网状ECM的多孔超微结构和更加理想的生物材料-组织融合度，与临床应用的胶原水凝胶Promogran™和Fibracol® Plus相比，普鲁兰-胶原水凝胶减少了巨噬细胞浸润和整体组织免疫反应，可加速小鼠创面修复和改善愈合后皮肤组织结构[9]。另一种天然多糖聚合物透明质酸，同样是ECM的重要成分，其促进创面修复的生物学效应主要由分子量决定。高分子量透明质酸可与单核细胞和粒细胞表面CD44受体结合，进而通过控制炎症细胞的募集、细胞因子的产生和干细胞的迁移而发挥抗炎作用；低分子量透明质酸主要通过促进血管生成，刺激促炎性细胞因子和生长因子产生，参与皮肤ECM重塑等[10]。丝素蛋白因具有优良的物理化学性能也被广泛用作诱导组织再生的结构材料，Guan等[11]研究表明，丝素蛋白水凝胶可通过踝蛋白1途径影响Fb、血管内皮细胞及KC的增殖、黏附和迁移能力，从而促进小鼠深Ⅱ度烧伤创面修复。丝素蛋白也可通过激活经典核因子κB信号通路，诱导多种生长因子的表达，这些生长因子主要作用于增殖和重塑阶段来促进小鼠创面修复。笔者课题组利用大鲵皮肤分泌物提取制备的水凝胶，因具有良好的组织黏附性能和生物活性，应用于大鼠全层皮肤缺损创面后，可促进血管生成和组织再生，从而促进创面快速闭合[12]。未来，可通过深入了解水凝胶基质材料成分如何影响创面修复过程，如干细胞分化、细胞异质性改变等，以及如何影响后续瘢痕形成及其结构重塑，进一步优化创面水凝胶敷料的性质。

2 水凝胶的特殊结构对创面修复的影响

聚合后的水凝胶因具有类似ECM的三维网状基质结构和类似皮肤软组织弹性等力学性能，可通过力学作用诱导细胞黏附、迁移及ECM沉积等，从而促进创面修复。水凝胶的微观结构参数(如含水量、交联密度、网孔尺寸等)可直接影响细胞生物学功能与行为，从而影响皮肤创面修复[5-6]。由于水凝胶是亲水聚合物，吸收大量水分后形成稳定的交联结构网络，因此，物理隔离和保湿作用是其成为创面敷料最基本的重要功能。创面湿润环境可减轻组织细胞脱水、保持细胞增殖和迁移活力、维持良好的创面愈合微环境、减缓创面进行性加深等，美国食品药品监督管理局批准创面修复用水凝胶产品的基本要求之一是具有良好的保湿和水化能力[13-14]。目前临床常用的水凝胶敷料(如

IntraSite®Gel、Flamigel®、Purilon®Gel 等），相较于传统敷料（如纱布、脱脂棉等），在维持创面愈合湿性平衡、促进自溶性清创与创面愈合、减轻换药疼痛等方面具有显著效果。研究表明，蛋白质类聚合物（如明胶、胶原、寡肽等）因溶解度有限，降低了其水凝胶支架长时间保持水分的能力，而水溶性多糖类（如透明质酸、壳聚糖、海藻酸钠等）及其衍生的聚合物因优良的长期保湿能力而在创面修复中应用得更为广泛[13]。创面敷料的保湿作用由其控制创面局部环境中的水分蒸发速度，即水蒸气透过率决定[14]。笔者课题组前期研究表明，通过调节创面敷料微观空间结构的孔隙率与孔径大小，使水蒸气透过率为 2 000 $g\cdot m^{-2}\cdot d^{-1}$ 左右时，创面敷料具有最显著的促进小鼠创面修复效果[15-16]。因此，可通过调节水凝胶的水蒸气透过率而调控其创面保湿效果，但需要根据创面类型、创面渗液量和修复阶段等选用合适水蒸气透过率的水凝胶，以达到更好地促进创面修复效果。也有学者直接将由羟甲基纤维素、丙二醇制备的无定形水凝胶应用于临床深Ⅱ度烧伤后磨削痂创面，观察到该水凝胶具有明显的保湿作用，可显著减轻换药时敷料与创面的粘连程度与患者疼痛，提高创面愈合率，降低创面感染率和手术植皮率，减少换药次数，缩短创面完全愈合时间，有效减轻瘢痕增生[17]。

水凝胶的宏观性能（如降解速率、机械强度等）可通过间接影响组织的整合和重塑而促进创面修复。近期，Griffin 等[18]研究表明，通过转换水凝胶结构中交联肽段的手性，调控水凝胶微球支架的降解速率，可更好地激活创面组织内适应性免疫反应，从而诱导包括毛囊在内的皮肤组织和附属器再生；Theocharidis 等[19]最近成功研制出程序化应变水凝胶贴片，它在干交联和水的形状记忆机制协同作用下，对创面产生稳定持续的机械力，精准控制创缘应力向中心聚集，从而使创面收缩，同时通过促进血管生成、上皮化及再生型 Fb 亚群的富集，实现了小鼠和猪糖尿病创面的快速修复。尽管已有大量研究集中于开发促进创面快速、高效修复的水凝胶，但关于水凝胶的具体结构、性能及其在诱导创面组织再生中的具体机制以及水凝胶-细胞组织间相互作用等科学问题仍需要进一步的深入研究。

3　复合特定功能的水凝胶促进创面修复

以创面治疗临床需求为出发点，水凝胶的功能迭代和新功能开发均有着广阔的探索空间。可通过对水凝胶结构域和特定官能基团等进行修饰，将各种优良性能集成一体，同时，可在水凝胶中负载不同活性分子，如药物、细胞因子、生长因子等及外源性细胞，如干细胞、上皮细胞、Fb 等，构建适用于创面修复的新型递送系统，从而更好地促进创面修复。近年来，大量研究聚焦于特定功能复合型水凝胶的研发，并取得了重要突破，本部分以典型的抗氧化等抗炎水凝胶、促进组织再生的水凝胶递送系统和抗感染水凝胶为例进行介绍。

3.1　抗氧化等抗炎水凝胶促进创面修复

合适炎症水平具有启动、促进创面修复的作用，但受各种病理因素影响，炎症反应程度过强或持续时间过长将导致创面修复延迟或停滞[20]。过度炎症往往伴随着炎症细胞募集和浸润增加，释放大量包括活性氧、趋化因子在内的多种炎症介质，形成促炎、高氧化应激、过度蛋白水解的创面微环境，加剧组织损伤，严重影响创面修复进程。调节创面炎症、降低创面氧化应激水平，有利于促进创面修复。目前，抗氧化等抗炎水凝胶主要通过清除过量活性氧、吸附隔离趋化因子和调控免疫细胞表型等机制发挥抗氧化及抗炎功效。笔者课题组成功研制了负载抗活性氧的含铜纳米酶肝素水凝胶，水凝胶基质中的肝素磺酸基团可有效吸附创面促炎和趋化因子，同时释放氧化铜纳米酶，高效清除创面局部活性氧，降低炎症细胞浸润等，有效促进小鼠急性和慢性创面修复[21]。Zhu 等[22]研制的生物活性玻璃-海藻酸钠水凝胶，可通过调节巨噬细胞与修复细胞之间的相互作用以及诱导巨噬细胞向 M2 表型极化，上调抗炎基因的表达，趋化 M2 型巨噬细胞在创面募集，并促进 Fb 和血管内皮细胞迁移，促进 ECM 合成和血管再生，从而促进小鼠创面快速愈合。

3.2　促进组织再生的水凝胶递送系统

创面修复过程涉及具有自分泌、旁分泌和内分泌功能的各种类型细胞之间的相互作用，也受创面内源性释放的生长因子、细胞因子和趋化因子等各种生物介质的严格调节。虽然在急性创面愈合过程中各种调控有序进行，但慢性创面均伴有不同程度的细胞数量不足和功能障碍以及生物介质水平失衡，外源性生物介质和细胞的局部递送成为慢性创面治疗的有效策略[23-24]。笔者课题组设计并以聚乙烯醇、海藻酸钠、壳聚糖为原料制备的载

P311 微球的温敏壳聚糖水凝胶复合体系，实现了 P311 的可控性释放并延长其作用时间，促进了小鼠创面血管生成及再上皮化[25]。Xu 等[26]利用超支化多丙烯酸聚乙二醇和硫酰化透明质酸制备干细胞递送水凝胶载体，负载脂肪源性干细胞后局部用于大鼠糖尿病创面，对维持干细胞活性、促进创面组织再生等有明显效果。泊洛沙姆 407 是具有良好安全性与生物相容性的三嵌段共聚物，含有亲水性的环氧乙烷单元和疏水性的环氧丙烷单元。泊洛沙姆 407 因具有特殊的逆向温敏性能，即当温度从 4 ℃提高到 37 ℃后，它将由溶胶状态聚合转变成凝胶状态，可用于制备局部可注射型水凝胶，作为递送药物、细胞、生物活性分子等的良好载体，用于治疗烧伤创面或其他组织损伤。笔者课题组近期设计制备了一种负载活性工程益生菌的多功能水凝胶，局部应用于小鼠糖尿病创面后，工程益生菌通过原位产生投递促血管再生因子与巨噬细胞表型调控分子，持续提供刺激血管再生信号并调控创面局部免疫反应；另外，经肝素修饰后的泊洛沙姆水凝胶进一步提高了促血管再生因子的生物利用度，从而重塑小鼠创面愈合微环境，增强创面血管再生能力，加快创面修复进程[27]。笔者课题组还利用从人层粘连蛋白-5α3 的球状结构域 3 获得的 PPLFMLLKGSTR 短肽，对泊洛沙姆结构进行功能化修饰，促进干细胞的黏附与存活；进一步负载环糊精纳米颗粒以降低局部炎症反应，从而成功构建一种可注射、机体温度触发交联、降低局部炎症反应/活性氧水平的多功能工程化水凝胶干细胞巢；再将外胚间充质干细胞负载其中，用于促进大鼠牙周炎所致牙槽骨破坏后的再生修复[28]。

3.3 抗感染水凝胶促进创面修复

感染是创面常见并发症，防止创面感染在创面修复中至关重要，抗感染水凝胶可能是防治创面感染的最好选择[29]。抗感染水凝胶可分为本身具有抗菌效能的水凝胶、含抗菌药物的水凝胶、刺激响应型抗菌水凝胶。以壳聚糖为代表的具有抗菌活性的水凝胶，其天然聚合物和相关衍生物中含有抗菌结构。壳聚糖单体的单氨基结构使其成为唯一的碱性多糖和酸性条件下带正电荷的多糖，因此可作为大多数细菌潜在的抑制剂。另外，壳聚糖水凝胶还具有合成简便、不良反应小和不需要额外添加抗菌成分等优势。为了增强壳聚糖的抗菌能力，可采用胺类、吡啶类、咪唑类、胍类和季铵盐等阳离子剂对其进行功能化修饰，使其产生更加强大而精准的抗菌效果。常用的抗菌剂有金属离子（如锌离子、铁离子、银离子）、金属纳米颗粒、抗生素和天然抗菌分子等[30]。Puthia 等[31]开发了基于凝血酶衍生 c 端 25 肽的水凝胶支架，凝血酶衍生 c 端 25 肽兼具良好的抗菌和下调炎症反应的作用，该水凝胶模拟人体宿主防御肽作用，在体外能够有效杀灭金黄色葡萄球菌、铜绿假单胞菌等多种临床菌株，对小鼠皮下感染和猪感染创面均有治疗效果。近年来，随着纳米医学的快速发展，融合光热、光动力等疗法，研发了许多刺激响应型抗感染水凝胶。光热疗法主要通过激光刺激光热材料（如石墨烯、聚多巴胺纳米颗粒）产生热效应，当温度超过 50 ℃时，细菌的细胞膜被破坏，最终导致细菌死亡。而光动力疗法主要依靠光敏剂在激光照射下产生活性氧，从而对细菌起到杀伤作用[32-33]。《中华烧伤与创面修复杂志》2022 年发表了应用具有 ECM 特性的甲基丙烯酸酐化明胶水凝胶负载银离子和重组人碱性 FGF 的研究，该复合水凝胶具有良好的抗菌性能，可显著促进兔深Ⅱ度烧伤创面上皮化与创面愈合[34]。

3.4 具有其他特殊功能的水凝胶促进创面修复

不同类型创面及创面愈合的不同阶段，需要应用不同功能的水凝胶。如烧伤即期需要进行及时有效的冷疗，从而阻断热对皮肤组织的损伤、减轻水肿、减少炎症介质产生与释放、减轻疼痛等，降温传热型水凝胶可能在冷疗中有着独特优势。Holzer 等[35]研制了高含水量细菌纳米纤维素水凝胶，该水凝胶可通过蒸发冷却效应达到冷疗的目的。也有研究者制备了含水量高达 95% 的聚乙烯醇-壳聚糖基水凝胶，该水凝胶可能成为烧伤创面冷疗敷料。这类研究利用水的高热容和蒸发潜热来制备具有冷却效应的水凝胶，但其冷却效率因水凝胶导热性受到限制，因此十分有必要开发一种集导热性和蓄热能力于一体，用于烧伤创面冷疗的新型水凝胶敷料。组织损伤后常出现不同程度出血，止血是创面早期急救的重要方面，由于水凝胶具有可塑形、可负载止血药物和良好的覆盖隔绝功能等优势，可能在创面急救中大有作为。笔者课题组将蛇毒血凝酶与伊红加入甲基丙烯酸修饰的明胶中，使其在可见光照射下迅速发生交联形成水凝胶，通过物理黏合、诱导血小板的聚集与活化，以及促进纤维蛋白原转化为纤维蛋白等机制，实现快速止血

和大鼠创面封闭[36]。当暴露在外部张力下或组织活动时，水凝胶的物理结构完整性容易被破坏，因此基于动态化学策略研发能够自行修复结构和功能的自修复水凝胶也是创面治疗的理想选择。笔者课题组前期利用聚丙烯酸羧基与铁离子之间的动态相互作用，成功研制出具有压敏性、导电性、可延展性、可用于三维打印的自修复水凝胶，可应用于多功能人工皮肤的制备[37]。

4　小结和展望

随着生物医学和材料科学等的发展与融合，研发高效、智能、微环境适应性的新型水凝胶为创面修复的治疗提供了新思路和新机遇。同时，由于创面修复过程是一个复杂而动态变化的生物学过程，很难用一种功能的水凝胶敷料同时满足整个过程的需要，因此需针对不同类型创面与创面修复的不同阶段，研制复合多种功能与疗效的水凝胶，以更方便地应用于临床创面修复。另外，实时监测创面微环境各项参数变化十分重要，制备可动态监测、智能响应的新型水凝胶将是今后的重要研究方向，以更精准、高效提高创面修复速度、改善创面修复质量。

利益冲突　所有作者均声明不存在利益冲突

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本刊可直接使用英文缩写的常用词汇

已被公知公认的缩略语如ATP、CT、DNA、HBsAg、Ig、mRNA、PCR、RNA，可不加注释直接使用。对本刊常用的以下词汇，也允许在正文中图表以外处直接使用英文缩写（按首字母排序）。

脱细胞真皮基质（ADM）
丙氨酸转氨酶（ALT）
急性呼吸窘迫综合征（ARDS）
天冬氨酸转氨酶（AST）
集落形成单位（CFU）
细胞外基质（ECM）
表皮生长因子（EGF）
酶联免疫吸附测定（ELISA）
成纤维细胞（Fb）
成纤维细胞生长因子（FGF）
3-磷酸甘油醛脱氢酶（GAPDH）
苏木精-伊红（HE）
重症监护病房（ICU）
白细胞介素（IL）
角质形成细胞（KC）
半数致死烧伤面积（LA50）
内毒素/脂多糖（LPS）
丝裂原活化蛋白激酶（MAPK）
最低抑菌浓度（MIC）
多器官功能障碍综合征（MODS）
多器官功能衰竭（MOF）
一氧化氮合酶（NOS）
负压伤口疗法（NPWT）
动脉血二氧化碳分压（$PaCO_2$）
动脉血氧分压（PaO_2）
磷酸盐缓冲液（PBS）
反转录-聚合酶链反应（RT-PCR）
全身炎症反应综合征（SIRS）
超氧化物歧化酶（SOD）
动脉血氧饱和度（SaO_2）
体表总面积（TBSA）
转化生长因子（TGF）
辅助性T淋巴细胞（Th）
肿瘤坏死因子（TNF）
血管内皮生长因子（VEGF）
负压封闭引流（VSD）

本刊编辑委员会

The Management of Radiation Induced Moist Desquamation using a Hydro-active Colloid Gel

Soni Shakya, Lead TVN, Simone Evans, TVN and Susan Winter, TVN - Musgrove Park Hospital, Somerset Foundation Trust.

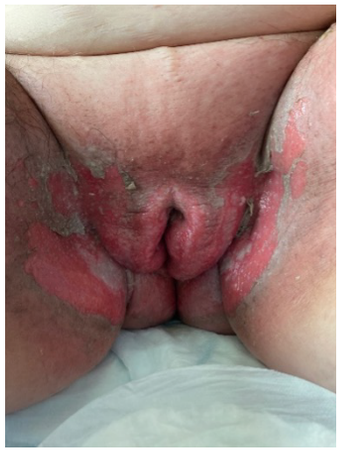
Introduction

Vulval cancer is a rare cancer with approximately 1,400 people diagnosed in the UK each year. It is more prevalent in older women with over 40% of new cases in those aged 75 years and above. Symptoms of the disease can be vague, particularly in the early stages and include a lasting itch, pain or soreness, thickened raised red, white or dark patches on the skin, a mole that changes colour or a noticeable lump. Diagnosis is usually detected with a combination of physical examination, imaging, including MRI and CT scans and biopsies. The main treatment options include surgery, radiotherapy and sometimes chemotherapy [1].

This case report involves an 83-year-old female who had a diagnosis of stage 2 vulval and perineal cancer and had undergone radical radiotherapy treatment to the vulva and the inguinal and pelvic nodes. Cancer is categorised into stage 1 to 4; stage 1 indicates that it is localised to the vulva and stage 2 classifies that it has spread to nearby tissue. Stage 3 and 4 shows that the cancer is advanced.

The patient had a previous medical history of Narcolepsy, total cholecystectomy, right oophorectomy, and partial gastrectomy.

Radiotherapy treatment commenced over a span of 35 days at which point the patient was referred to the Tissue Viability Specialist Nurse for support with managing the skin reaction. Radiotherapy induced dermatitis is categorised from 0-4 (inclusive of 2a & 2b) as classified by the Radiotherapy Oncology Group (RTOG) grading system [2].



Day 0 - Pain, excoriation

Day 10 - on discharge, reduced pain and self-managing

Unfortunately, the Tissue Viability Nurse did not have access to the radiotherapy notes, where skin reactions would have been documented and therefore the RTOG was not applied.

The Tissue Viability Nurse verified moist desquamation skin reaction to the vulva, perinium, groins and inner thighs. This describes an Inflammatory reaction characterised by blistering, peeling and sloughing of the skin and can have a shiny or wet appearance. The patient was suffering with associated pain and there were moderate volumes of exudate.

The previous treatment plan had consisted of lidocaine primary dressing and secondary superabsorbent, glycerine impregnated dressing; inclusive of the use of an additional ointment-based emollient.

Method

The Tissue Viability Specialists aims were to reduce pain, manage exudate and promote healing. There were no obvious clinical signs of infection at the point of the initial review. The patient had stated that the previous dressing regimen was uncomfortable and impractical, due to frequency of dressing changes to accommodate toileting needs.
A hydro-active colloid gel (Flamigel® RT) was commenced with the advice to apply post toileting with a secondary continence pad. Self-management was encouraged and the patient did most of her care independently.

Result

The use of hydro-active colloid gel (Flamigel® RT) continued for a period of 10 days. There was a noticeable decrease in exudate levels, less inflammation, an increase in the formation of granulation tissue and a general reduction in the overall size of the affected skin with increased healing.
The patient expressed that from the commencement of Flamigel® RT, the previously experienced pain had significantly reduced, and she declined any further use of Lidocaine. At the point of the discharge home, day 10 of treatment, the patient was self-managing her radiotherapy skin reaction with minimal support which evidently heightened her confidence and improved her quality of life.

Discussion

Acute skin reactions associated with radiotherapy can be distressing and can lead to treatment interruptions. Such skin reactions are very common, affecting 80-100% of patient undergoing adjuvant or curative radiotherapy. Most patients have mild reactions, however, some, including those having radiotherapy to the head and neck or pelvic area, experience more severe reactions. The importance of anticipating, assessing, and managing the problem in line with best clinical evidence can increase the chance of a successful outcome for the patient [3].

Conclusion

Living with painful, wet skin erosion, rising from radiotherapy, can be debilitating and can often result in the interruption, due to intolerance, of vital lifesaving treatment. This case study demonstrates the effectiveness of Flamigel® RT in the management of such skin reactions, in particular moist desquamation. The Tissue Viability Nurse implemented this product, following careful consideration of its properties coupled with available clinical evidence validating the successful outcomes previously achieved for its use with induced dermatitis skin conditions. The study also highlights the importance of an assessment combined with appropriate management (including self-management) to achieve the best clinical outcome.

The Tissue Viability Nurse concluded that the treatment aims were achieved, and the patient's clinical outcome and quality of life improved as result of this.

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advanced skin healing