

Consensus guidelines for the management of radiation dermatitis and coexisting acne-like rash in patients receiving radiotherapy plus EGFR inhibitors for the treatment of squamous cell carcinoma of the head and neck

J. Bernier^{1*}, J. Bonner², J. B. Vermorken³, R.-J. Bensadoun⁴, R. Dummer⁵, J. Giralt⁶, G. Kornek⁷, A. Hartley⁸, R. Mesia⁹, C. Robert¹⁰, S. Segaert¹¹ & K. K. Ang¹²

¹Department of Radiation Oncology, Genolier Swiss Medical Network, Genolier, Geneva, Switzerland; ²Department of Radiation Oncology, The University of Alabama at Birmingham, Birmingham, Alabama USA; ³Department of Oncology, Universitair Ziekenhuis Antwerpen, Edegem, Belgium; ⁴Department of Radiation Oncology, Centre Antoine-Lacassagne, Nice, France; ⁵Dermatologische Klinik, Universitätsspital Zurich, Zurich, Switzerland; ⁶Department of Radiation Oncology, Vall d'Hebron University Hospital, Barcelona, Spain; ⁷Medizinische Universität Vienna, Universitätsklinik Innere Medizin I Klinische Abteilung für Onkologie, Vienna, Austria; ⁸The Cancer Centre, Queen Elizabeth Hospital, Birmingham, UK; ⁹Department of Medical Oncology, Institut Català d'Oncologia-L'Hospitalet, Barcelona, Spain; ¹⁰Service de Dermatologie, Institut Gustave Roussy, Villejuif Cedex, France; ¹¹Department of Dermatology, University Hospital Leuven, Leuven, Belgium; ¹²Gilbert H. Fletcher Memorial, M.D. Anderson Cancer Center, University of Texas, Houston, Texas, USA

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Background: Radiation dermatitis occurs to some degree in most patients receiving radiotherapy, with or without chemotherapy. Patients with squamous cell carcinoma of the head and neck (SCCHN) who receive radiotherapy in combination with epidermal growth factor receptor (EGFR) inhibitors, such as cetuximab, may develop a characteristic acne-like rash in addition to dermatitis.

Design: An advisory board of 11 experienced radiation oncologists, medical oncologists and dermatologists discussed the management options for skin reactions in patients receiving EGFR inhibitors and radiotherapy for SCCHN. Skin toxicity was categorised according to the National Cancer Institute—Common Terminology Criteria for Adverse Events (version 3) grading.

Results: Both general and grade-specific approaches for the management of dermatitis in this patient group are presented. It was concluded that where EGFR inhibitor-related acne-like rash and dermatitis coexist within irradiated fields, management should be based on the grade of dermatitis: for grade 1 (or no dermatitis), treatment recommendations for EGFR-related acne-like rash outside irradiated fields should be followed; for grades 2 and above, treatment recommendations for dermatitis were proposed.

Conclusions: This paper presents comprehensive consensus guidelines for the treatment of dermatitis in patients with SCCHN receiving EGFR inhibitors in combination with radiotherapy.

Key words: cetuximab, EGFR inhibitors, radiation dermatitis, radiotherapy, skin reactions, squamous cell carcinoma of the head and neck

Introduction

External beam radiotherapy is the main nonsurgical treatment in patients with locoregionally advanced head and neck cancers. The acute side-effects of radiation therapy are well documented and include dermatitis, mucositis, xerostomia, weight loss, dysphagia, taste alteration, nausea and vomiting, pain and asthenia. When given without chemotherapy, altered

fractionation regimens, including accelerated and hyperfractionated regimens, alone or combined [1], have largely replaced conventional radiation fractionation (70 Gy in 2 Gy fractions over a 7-week period). Reducing overall treatment time and/or increasing total radiation dose have improved locoregional control, although effects on overall survival were less significant [1, 2]. The improvements in locoregional control, however, are achieved at the expense of an increase in acute toxicity [1–3]. In a randomised phase III Radiation Therapy Oncology Group (RTOG) study (RTOG 9003), the incidence of grade 3 or worse acute side-effects was

*Correspondence to: Dr J. Bernier, Department of Radiation Oncology, Genolier Swiss Medical Network, CH-1272 Genolier, Switzerland. Tel: +41-22-366-9959; Fax: +41-22-366-9961; E-mail: jacques.bernier@hcuge.ch

35% for conventional fractionation and 54.5%, 50.4% and 58.8% for hyperfractionation, split-course accelerated fractionation and accelerated fractionation with concomitant boost, respectively [1].

radiation dermatitis

Radiation dermatitis is experienced, to various degrees, by the majority of patients undergoing radiotherapy for locoregionally advanced head and neck cancer (Table 1) [1, 2, 4–8]. In most patients, the radiation dermatitis is mild to moderate (grades 1 and 2), but ~20%–25% of patients experience severe reactions [9]. The incidence of severe reactions is dependent on the total radiation dose, the dose per fraction, the overall treatment time, beam type and energy and the surface area of the skin that is exposed to radiation [10]. In the RTOG 9003 study, the rates of acute grade 3/4 skin toxicity were slightly higher with hyperfractionation (11%) and accelerated fractionation with concomitant boost (11%) compared with standard fractionation (7%). It is well recognised that the addition of chemotherapy to radiotherapy (chemoradiotherapy) increases the acute side-effect profile of treatment [6, 11], particularly when combined with altered fractionation regimens. In a recently reported phase III study, in which the majority of patients received > 60 Gy with concomitant boost regimen, and 53% of patients also received

chemoradiotherapy [12], the mean rates of grades 2, 3 and 4 radiation dermatitis were 54%, 20% and 4%, respectively [12]. The authors contrasted these rates with the corresponding rates of 49%, 8% and 0% observed over all arms of the RTOG 9003 study [1, 12]. The severity of acute reactions has been shown both to lead to enhanced late effects and to impact adversely on cosmesis, especially in patients with infected irradiated skin [13]. Finally, an association between the occurrence of radiation dermatitis and patient quality of life has been observed [12], and the impact of this on the well-being of the patient should not be underestimated.

grading of radiation dermatitis

Radiation dermatitis generally manifests within a few weeks after the start of radiotherapy. Its onset varies depending on the radiation dose intensity and the normal tissue sensitivity of individuals. As the cumulative dose of radiation increases, the transient erythema occurring during the first weeks of radiotherapy may evolve into the more persistent erythema to dry or even moist desquamation that reflects the damage to the basal cell layer and the sweat and sebaceous glands. A number of different systems have been developed by various organisations over the years (see Table 1), including the National Cancer Institute (NCI), the RTOG, World Health

Table 1. Incidence of grade 3+ radiation-associated skin toxic effects in patients receiving different radiotherapy regimens for head and neck cancers in randomised phase III trials

Type of RT	Dosing regimen	N	Toxicity grading scale	Grade 0–2 skin toxicity (%)	Grade ≥ 3 skin toxicity (%)	References
Conventional	70 Gy (35 2-Gy fractions in 7 weeks)	113	EORTC	47	11 (grade 3)	Calais et al. [5]
		129	RTOG	73	27 (epidermitis)	Bourhis et al. [2]
		268	RTOG	94	7 (grade 3)	Fu et al. [1]
Accelerated RT	70.2 Gy (39 1.8-Gy fractions in 51 days) three cycles of 23.4 Gy each, separated by a rest period of 11 days	140	WHO	Not reported	6.4 (grade 3), 0.7 (grade 4)	Wendt et al. [6]
Accelerated RT with split	67.2 Gy (42 1.6-Gy fractions b.i.d., 5 days/week in 6 weeks including a 2-week rest after 38.4 Gy)	274	RTOG	85	3 (grade 3)	Fu et al. [1]
Very accelerated RT	62–64 Gy (31–32 2-Gy fractions in 23 days)	137	RTOG	66	33 (epidermitis)	Bourhis et al. [2]
Accelerated RT with concomitant boost	72 Gy (42 1.8-Gy fractions, 5 days/week >6 weeks with concomitant boost of 1.5 Gy/fraction/day for the final 12 treatment days)	268	RTOG	85	11 (grade 3)	Fu et al. [1]
Hyperfractionated RT	81.6 Gy (68 1.2-Gy fractions b.i.d., 5 days/week in 7 weeks)	263	RTOG	81	11 (grade 3), <1 (grade 4)	Fu et al. [1]
Hyperfractionated accelerated RT	77.6 Gy in 6 weeks (2.0 Gy q.i.d. to 14 Gy then 1.4 Gy b.i.d.)	177	EORTC	Not reported	46 (grade 3/4)	Budach et al. [7]
IMRT (not randomised)	Definitive IMRT (n = 52) ^a : mean dose 64.34–72.64 Gy; postoperative IMRT (n = 74): 60.95–68.53	126	RTOG	75	18 (grade 3), 7 (grade 4)	Chao et al. [8]

Unless otherwise stated, data are presented only for the trial arms in which patients received RT alone.

^aThirty five patients received concomitant cisplatin.

EORTC, European Organisation for Research and Treatment of Cancer; IMRT, intensity-modulated radiotherapy; RT, radiotherapy; RTOG, Radiation Therapy Oncology Group; WHO, World Health Organisation.

Organisation and the European Organisation for Research and Treatment of Cancer, to describe the spectrum of radiation dermatitis. The need for the development and implementation of meaningful and reliable reporting methods for recording and reporting the toxicity of cancer treatment, which will also enable the comparison of toxicity between centres, is well recognised [14]. Of the currently available toxicity criteria, those introduced by the NCI in 2003 [NCI—Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3] are considered to be the most comprehensive method [14, 15]. The grading of radiation dermatitis according to these criteria is shown in Table 2.

pathophysiological characteristics of radiation dermatitis

Irradiation of the skin leads to a complex pattern of direct tissue injury and inflammatory cell recruitment, involving damage to epidermal basal cells, endothelial cells and vascular components and a reduction in Langerhans cells [10] (and references contained therein). Radiation-induced keratinocyte damage induces DNA injury repair via activation of the p53 pathway and a simultaneous release of inflammatory cytokines as a consequence of the generation of free radicals. The main cytokines involved in this reaction are interleukins 1 and 6, tumour necrosis factor- α and transforming growth factor- β [16]. At the same time, keratinocytes demonstrate increased expression of epidermal growth factor receptor (EGFR), possibly as a mechanism for repopulating irradiated areas [17]. The up-regulation of EGFR may alter the cells interaction with EGFR inhibition, although cetuximab in combination with radiation has not exacerbated radiation dermatitis in clinical trials to date [9]. In severe radiation dermatitis, there is massive neutrophilic infiltration of the epidermis and profound apoptosis. With successive doses of radiation, the opportunity for tissue healing due to cellular repopulation is reduced, even over weekend interruptions of daily fractionated radiotherapy, thereby compounding the insult. Chronic radiation-induced changes in the skin are characterised by the disappearance of follicular structures, an increase in collagen and damage to elastic fibres in the dermis, and a fragile epidermal covering.

EGFR inhibitors in squamous cell carcinoma of the head and neck

EGFR inhibitors are increasingly being used in a range of tumour types in combination with standard therapies in an attempt to improve outcome. In 2006, the results of

a randomised phase III study demonstrated that the addition of the EGFR-targeted IgG1 mAb, cetuximab, to radiotherapy resulted in statistically significant and clinically meaningful improvements in the duration of locoregional control and median overall survival versus radiotherapy alone in the treatment of locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN) [9]. This study led to the regulatory approval in a number of countries of cetuximab plus radiotherapy in this setting.

skin reactions associated with EGFR inhibitors

EGFR inhibitor use can be associated with the development of skin reactions, including a macular, papular, pustular rash, commonly referred to as acne-like rash (or folliculitis); xerosis; fissures; telangiectasia; hyperpigmentation and hair and nail changes [18]. The most common skin reaction is the acne-like rash [18, 19], which is generally distributed in areas rich in sebaceous glands, such as the face, neck and retroauricular area, the shoulders, the upper trunk (V-shaped) and the scalp [18]. The acne-like rash comprises itchy erythematous follicular papules that may evolve into pustules which may conflate [18]. Other presentations include: diffuse erythema with follicular papulopustules and telangiectasia, a seborrhoeic dermatitis-like rash or, occasionally, an oedematous facial erythema [18]. In the absence of radiation, the acne-like rash can be seen within a few days of the commencement of treatment and peaks at 2–3 weeks after starting therapy. In some cases, the rash can be delayed, and in others flares can occur at each subsequent administration of the EGFR inhibitor. The majority of skin reactions seen with cetuximab are grade 1 or 2 (~80%) [20] and often resolve without the need for specialised treatment.

The pathophysiology of the skin reactions associated with EGFR inhibitors is still not well understood [21]. The EGFR is expressed at high levels in the epidermis and in the hair follicle, particularly in the proliferative basal cell layers, and EGFR is known to be essential to the regulation of several aspects of normal keratinocyte biology, including cell cycle progression, differentiation, cell movement and cellular survival [22]. Systemic administration of cetuximab results in up-regulation of the negative growth regulator, p27^{kip}, in epidermal keratinocytes, possibly leading to impairment of cell growth and differentiation [23]. In patients developing EGFR inhibitor-associated acne-like rash, basal keratinocytes in the epidermis and hair follicles display high levels of p53. In addition, inflammation is commonly found in the epidermal–dermal junction, accompanied by neutrophilic infiltration and damage to hair follicles.

Table 2. Toxicity grading of radiation dermatitis according to the National Cancer Institute—Common Terminology Criteria for Adverse Events (version 3) [15]

Adverse event	Short name	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash: dermatitis associated with radiation	Dermatitis	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate oedema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site	Death

Beneficial topical treatment approaches include anti-inflammatory or antibiotic medication, supplemented with saline compresses for grade 3 reactions [18], oral tetracyclines for grade 2+ reactions, with an appropriate antibiotic for *Staphylococcus aureus* superinfection, and oral antihistamines to reduce pruritus. The long-term use of corticosteroids is generally avoided due to their potential to induce or exacerbate acne and other skin conditions and to interfere with the antibody-dependent cell-mediated cytotoxicity reactions thought to contribute to the antitumour effects of cetuximab [18].

radiation dermatitis in patients receiving radiotherapy and EGFR inhibitors

Considering the fact that radiation is known to up-regulate EGFR in unirradiated skin, it would appear possible that there is some biological interplay between the pathophysiological effects of radiation on the skin and those of EGFR inhibitors. Coupled with preclinical findings showing that cetuximab demonstrates marked synergy with radiation in cancer cell lines and tumour models [24–26], the effect on the skin of a combination of cetuximab and radiation is of considerable interest, as it might require special care to reduce symptoms and severity. Interestingly, radiation appears to delay the onset of the cetuximab-induced acne-like rash. The cetuximab-associated acne-like rash typically appears within irradiated fields ~3–5 weeks after initiation of treatment [27]. There appears to be no obvious relationship between the severity of cetuximab-associated acne-like rash outside irradiated fields and the severity of radiation dermatitis.

The phase III randomised trial comparing radiotherapy with or without cetuximab in locoregionally advanced SCCCHN revealed no statistically significant increase in the incidence or severity of radiation dermatitis compared with radiotherapy alone (Table 3) [9]. The incidence of grade ≥ 3 radiation dermatitis was 18% with radiotherapy alone and 23% with radiotherapy plus cetuximab ($P = 0.27$). There was a slight increase in the median duration of radiation dermatitis in the cetuximab arm (11.1 weeks) compared with the radiotherapy-alone arm (9.4 weeks) [27].

the management of radiation dermatitis in patients receiving radiotherapy and EGFR inhibitors

Centres at which radiotherapy is routinely administered for the treatment of SCCCHN have institutional policies on the management of radiation dermatitis. Gentle washing and drying of the skin within the radiation portal have been shown to reduce the acute radiotherapy-associated skin reactions in patients receiving radiotherapy for breast cancer and is now routinely recommended for all patients receiving radiotherapy [28, 29]. Beyond that, there is little evidence to support the use of one topical approach over another, as highlighted by recent literature reviews of trials investigating the prophylaxis and treatment of radiation dermatitis for various tumour types [30, 31]. The recently reported results of an RTOG trial (99-13) in patients with SCCCHN failed to show any benefit of the systematic use of interventional or prophylactic trolamine emulsion in reducing grade 2 or higher skin toxicity [12]. Another study showed no

Table 3. Incidence of grade 3/4 radiation dermatitis with radiotherapy \pm cetuximab in locoregionally advanced squamous cell carcinoma of the head and neck: data from a randomised phase III trial [9]

Type of RT	Dosing regimen	N = 424	All grades (%)		Grade ≥ 3 (%)	
			RT alone (N = 212)	RT + cetuximab (N = 208)	RT alone (N = 212)	RT + cetuximab (N = 208)
Once daily	70 Gy (35 2-Gy fractions in 7 weeks)	26%	90	86	18	23
Twice daily	72–76.8 Gy in 60–64 fractions (10 1.2-Gy fractions for 6–6.5 weeks)	18%				
Concomitant boost	72 Gy in 42 fractions (Once-daily fractions; 1.8 Gy/fraction; 5 fractions/week for 3.6 weeks: twice-daily fractions; AM 21.6 Gy, 1.8 Gy/fraction, 5 fractions/week for 2.5 weeks. PM 18.0 Gy, 1.5 Gy/fraction, 5 fractions/week for 2.4 weeks)	56%	$P = 0.24^a$		$P = 0.27^a$	

Toxicity assessed using Radiation Therapy Oncology Group toxicity scale; P value determined with the use of Fisher's exact test. RT, radiotherapy.

^aRT alone vs RT + cetuximab, where RT includes once daily, twice daily and concomitant boost regimens.

significant benefit of pentoxifylline prophylaxis on the development of acute skin reactions [32]. The potential benefit of oral zinc supplementation in postponing the development of severe mucositis and dermatitis, and in alleviating the degree of mucositis and dermatitis, in patients receiving radiotherapy for cancers of the head and neck [33] warrants additional confirmatory studies.

The goal of the advisory board meeting reported here was to develop consensus guidelines to help physicians effectively manage radiation dermatitis in patients receiving radiotherapy and concurrent EGFR inhibitor treatment for SCCHN. The advisory board panel comprised 11 specialists from seven countries in the fields of radiation and medical oncology and dermatology.

The major aim of managing skin reactions within irradiated areas is to minimise modification of the prescribed radiotherapy and/or EGFR inhibitor regimens, which might compromise efficacy. It is important to recognise that the choice of radiotherapy dose and schedule is at the discretion of the radiation oncologist and should not be influenced, in the absence of compelling data, by the concomitant administration of the EGFR inhibitor. While there is an increase in acute toxicity associated with altered fractionation, relative to conventional fractionation, there are no data to indicate that EGFR inhibitors, such as cetuximab, cannot be used with altered fractionation regimens. In fact, a majority of patients received altered fractionation regimens in combination with cetuximab in the recent phase III trial comparing combination treatment with radiotherapy alone [9].

General management of radiation dermatitis is presented along with treatment measures according to the NCI CTCAE (version 3) grading of dermatitis (Table 4), divided into three categories, i.e. grade 1, grades 2–3 and grade 4.

General management

- While the development of some degree of radiation dermatitis is considered inevitable for the majority of patients receiving radiotherapy, the establishment of a proper technique to minimise the dose delivered to the epidermis and a quality assurance programme for radiotherapy planning and delivery is critical not only in therapeutic terms but also from the perspective of avoiding unnecessary skin toxicity.
- A primary step in the management of radiation dermatitis of any grade is to establish that the skin reactions are not a result of any concomitant medication, other than the EGFR inhibitor. In the case of more severe skin reactions, it should also be verified that radiation dose and distribution are correct.

Following these actions, a number of steps, irrespective of the grade of radiation dermatitis, can be followed.

- It is recommended that the institutional policy for skin preparation before radiotherapy be adopted for patients scheduled to receive an EGFR inhibitor and radiotherapy. Patients should be encouraged to maintain good standards of hygiene. The irradiated area should be kept clean to minimise the risk of infection. Patients should wash the area

with a gentle cleanser and dry it with a soft, clean towel. The use of a pH-neutral synthetic detergent is preferable to soap, which can irritate the skin.

- Topical treatment approaches may offer symptomatic relief and may help skin healing. Different areas of skin may require different treatment approaches.
 - Drying pastes may be appropriate for use within skin folds, where skin reactions remain moist.
 - Gels can be useful in seborrhoeic areas.
 - Creams can be used in areas outside skin folds and seborrhoeic areas.
 - Hydrophilic dressings may also be useful in moist areas. These are placed over the cleaned, dried wound and some can absorb wound exudate. They can be soothing for the patient and can help skin healing.
 - Greasy topical products should be avoided because they inhibit the absorption of wound exudate and promote superinfection.

Topical moisturisers, gels, emulsions and dressings should not be applied shortly before radiation treatment as they can cause a bolus effect, thereby artificially increasing the radiation dose to the epidermis. It is important to instruct patients to gently clean and dry the skin in the radiation field before each irradiation session.

- While the use of corticosteroids, often applied in some centres during the course of radiotherapy in head and neck cancer patients, is not contra-indicated in the presence of radiation dermatitis, it is suggested that the overall treatment time of any corticosteroid-containing treatment be limited.
- Pain relief for skin reactions should be considered in the context of any pain relief medication the patient may already be receiving in the course of their treatment, for instance, for mucositis.
- Patients should be advised to avoid:
 - Sun exposure wherever possible. This can be achieved by using soft clothing to cover the area and/or the use of mineral sunblocks.
 - The use of skin irritants, such as perfumes, deodorants or alcohol-based lotions.
 - Scratching of the skin in the affected area.
- General guidance on the treatment of cetuximab-associated skin reactions developing outside the irradiated area was reported elsewhere [18–20].

prophylaxis

There is currently no evidence that prophylactic treatments, beyond keeping the irradiated area clean and dry, are effective in reducing the incidence or severity of radiation dermatitis [31].

grade 1 radiation dermatitis

The NCI CTCAE (version 3.0) definition of grade 1 radiation dermatitis is faint erythema or dry desquamation [15]. Grade 1

Table 4. Grade-specific management of radiation dermatitis in patients with squamous cell carcinoma of the head and neck receiving radiotherapy and cetuximab: a summary

Grade of radiation dermatitis	Grade 1	Grade 2	Grade 3	Grade 4
Definition of radiation dermatitis (NCI CTCAE, v3.0)	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy, moist desquamation, mostly confined to skin folds and creases; moderate oedema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Skin necrosis or ulceration of full thickness of dermis; spontaneous bleeding from involved site
General management approaches	See General management Maintain hygiene and gently clean and dry skin in the radiation field shortly before radiotherapy Topical moisturisers, gels, emulsions and dressings should not be applied shortly before radiation treatment as they can cause a bolus effect, thereby artificially increasing the radiation dose to the epidermis			
Grade-specific management approaches	Use of a moisturiser is optional If anti-infective measures are desired, antibacterial moisturisers (e.g. triclosan or chlorhexidine-based cream) may be used occasionally	Keep the irradiated area clean, even when ulcerated In the absence of clinical signs of infection, one or combinations of the following topical approaches may be used: <ul style="list-style-type: none"> • Drying gels, possibly with the addition of antiseptics (e.g. chlorhexidine-based creams) • An anti-inflammatory emulsion, such as trolamine • Hyaluronic acid cream • Hydrophilic dressings, applied after radiotherapy to the cleaned, irradiated area, which may provide symptomatic • Zinc oxide paste, if easy to remove prior to radiotherapy • When used, silver sulfadiazine or beta glucan cream should be applied after radiotherapy (possibly in the evening) after cleaning the irradiated area • Where infection is suspected: <ul style="list-style-type: none"> • The treating physician should use best clinical judgement for identifying infection, including the consideration of swabbing the area for identification of the infectious agent • Topical antibiotics (should not be used prophylactically) • Doxycycline is not recommended at this stage • Blood granulocyte counts should be checked, particularly if the patient is receiving concomitant chemotherapy • Blood cultures should be carried out if there are additional signs of sepsis and/or fever 	Verify that radiation dose and distribution are correct Requires specialised wound care with the assistance of the radiation oncologist, dermatologist and nurse, and should be treated on a case by case basis	
Management team	Can be managed primarily by nursing staff	Can be managed by an integrated management team comprising the radiation oncologist, nurse, medical oncologist (where appropriate) and dermatologist, as required Skin reactions should be assessed at least once a week		Should be managed primarily by a wound specialist, with the assistance of the radiation oncologist, medical oncologist (where appropriate), dermatologist and nurse, as required

Please see text for full details. NCI CTCAE, National Cancer Institute—Common Terminology Criteria for Adverse Events.

radiation dermatitis requires no specific treatment. Indeed, the most important step is to keep the area clean between treatments. The subsequent use of a nonperfumed moisturiser is optional. Moisturisers containing antibacterials (e.g. chlorhexidine or triclosan) can be used occasionally if anti-infective measures are considered appropriate. Overtreatment, including overuse of antiseptic creams, can irritate the skin. In general, skin reactions at this grade can be managed primarily by the nursing staff.

grades 2 and 3 radiation dermatitis

According to the NCI CTCAE (version 3.0) classification, grade 2 radiation dermatitis includes moderate to brisk erythema, patchy moist desquamation mostly confined to skin folds and creases and moderate oedema [15]. Grade 3 radiation dermatitis consists of moist desquamation other than skin folds or creases and bleeding induced by minor trauma or abrasion [15].

In grades 2 and 3 radiation dermatitis, as with grade 1, the irradiated area should be cleaned and dried, even when ulcerated. A number of topical applications can be considered. Examples are drying gels, with the addition of antiseptics if considered appropriate (e.g. chlorhexidine-based creams, but not chlorhexidine in alcohol), hydrophilic dressings, an anti-inflammatory emulsion (e.g. trolamine, hyaluronic acid cream) and zinc oxide paste, if considered sufficiently easy to remove before radiotherapy. Silver sulfadiazine or beta glucan cream may also be useful (but should only be applied after radiotherapy, possibly in the evening, after cleaning the irradiated area).

Where infection is suspected, the treating physician should use best clinical judgement for management, including considering swabbing the affected area for identification of the infectious agent. Topical antibiotics should be reserved for superinfection and should not be used prophylactically. Doxycycline is not recommended at this stage. In patients in whom skin infection is suspected or documented, the blood granulocyte count should also be checked, especially if the patient is also receiving concomitant chemotherapy. Indeed, severe desquamation is associated, in a number of cases, with a risk of septicaemia. Blood cultures should also be carried out if additional signs of sepsis and/or fever are present, particularly if the granulocyte count is low.

Grades 2 and 3 radiation dermatitis can be managed by an integrated team comprising the radiation oncologist, medical oncologist (where appropriate), nurse and dermatologist, as required. Skin reactions should be assessed at least once a week.

grade 4 radiation dermatitis

Grade 4 radiation dermatitis is defined by the NCI CTCAE (version 3.0) as skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from the involved site [15]. Grade 4 radiation dermatitis is relatively rare, generally occurring in <5% of patients receiving radiotherapy for SCCHN. This stage of radiation dermatitis requires specialised wound care and should be treated on a case-by-case basis. Grade 4 radiation dermatitis should be managed primarily by a wound specialist, with the assistance of the radiation

oncologist, medical oncologist (where appropriate), dermatologist and nurse, as required.

the management of coexisting radiation dermatitis and EGFR inhibitor-related acne-like rash within irradiated fields

Where there is coexistence of radiation dermatitis and EGFR inhibitor-related acne-like rash within an irradiated field, management depends on the grade of radiation dermatitis:

- For grade 1 radiation dermatitis (or no radiation dermatitis), it is prudent to follow the published general guidelines on the management of EGFR inhibitor-related acne-like rash outside irradiated fields [18–20].
- For grade 2 or higher radiation dermatitis, it is preferable to adhere to the management recommendations for radiation dermatitis, as outlined in this manuscript.

issues to be addressed

One of the problems hindering the effective reporting and management of acute radiation toxic effects, including radiation dermatitis, is, as discussed earlier, the use of varied, inconsistent toxicity criteria. The adoption of the NCI CTCAE version 3 by an increasing number of institutions is a step forward in achieving consistency in toxicity reporting. However, even with the use of standardised criteria, grading of reactions remains subjective and this will impede the interpretation of toxicity findings between clinical studies. One way to minimise discrepancy is to document skin toxicity photographically, thus enabling subsequent independent confirmation of gradings where necessary. It is recommended that digital photographic documentation be adopted as a standard practice in clinical trials.

It is clear that while commonly used topical products may help to manage the symptoms of radiation dermatitis and EGFR inhibitor-associated acne-like rash, there is little evidence to indicate that any of the currently available products can prevent the development of these skin reactions. Recently, the topical application of vitamin K3 (menadione), an EGFR phosphatase inhibitor, was shown to restore EGFR-mediated signalling in the skin secondary to systemic administration of the EGFR inhibitors, erlotinib and cetuximab [34]. In view of this, it would be interesting to formally test whether prophylactic application of menadione within a radiation field would alter the incidence, intensity and/or characteristics of EGFR inhibitor-associated acne-like rash developing within the irradiated field in patients receiving cetuximab and radiotherapy.

A greater understanding of the biological mechanisms responsible for the skin toxicity of the individual agents would lead to the development of rational and more effective management strategies for the skin reactions of patients receiving radiotherapy and EGFR inhibitors. The toxicity of the combination of cetuximab and radiotherapy in the clinical setting is being further studied in preclinical models and is being monitored in the ongoing pharmacovigilance

programme. In addition, results from clinical trials currently being conducted by, among others, the RTOG and the French radiotherapy oncology group for head and neck cancer should provide more information on any toxicity interactions between the two treatments.

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references

1. Fu KK, Pajak TF, Trotti A et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 2000; 48: 7–16.
2. Bourhis J, Lapeyre M, Tortochaux J et al. Phase III randomized trial of very accelerated radiation therapy compared with conventional radiation therapy in squamous cell head and neck cancer: a GORTEC trial. *J Clin Oncol* 2006; 24: 2873–2878.
3. Zackrisson B, Mercke C, Strander H et al. A systematic overview of radiation therapy effects in head and neck cancer. *Acta Oncol* 2003; 42: 443–461.
4. Burtess B, Goldwasser MA, Flood W et al. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 2005; 23: 8646–8654.
5. Calais G, Alfonsi M, Bardet E et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst* 1999; 91: 2081–2086.
6. Wendt TG, Grabenbauer GG, Rodel CM et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter study. *J Clin Oncol* 1998; 16: 1318–1324.
7. Budach V, Stuschke M, Budach W et al. Hyperfractionated accelerated chemoradiation with concurrent fluorouracil-mitomycin is more effective than dose-escalated hyperfractionated accelerated radiation therapy alone in locally advanced head and neck cancer: final results of the radiotherapy cooperative clinical trials group of the German Cancer Society 95-06 prospective randomized trial. *J Clin Oncol* 2005; 23: 1125–1135.
8. Chao KS, Ozyigit G, Thorsdad WL. Toxicity profile of intensity-modulated radiation therapy for head and neck carcinoma and potential role of amifostine. *Semin Oncol* 2003; 30: 101–108.
9. Bonner JA, Harari PM, Giralt J et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006; 354: 567–578.
10. Hymes SR, Strom EA, Fife C. Radiation dermatitis: clinical presentation, pathophysiology, and treatment 2006. *J Am Acad Dermatol* 2006; 54: 28–46.
11. Adelstein DJ, Li Y, Adams GL et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol* 2003; 21: 92–98.
12. Elliott EA, Wright JR, Swann RS et al. Phase III trial of an emulsion containing trolamine for the prevention of radiation dermatitis in patients with advanced squamous cell carcinoma of the head and neck: results of Radiation Therapy Oncology Group Trial 99-13. *J Clin Oncol* 2006; 24: 2092–2097.
13. Dorr W, Hendry JH. Consequential late effects in normal tissues. *Radiother Oncol* 2001; 61: 223–231.
14. Trotti A, Bentzen SM. The need for adverse effects reporting standards in oncology clinical trials. *J Clin Oncol* 2004; 22: 19–22.
15. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). <http://ctep.cancer.gov/forms/CTCAEv3.pdf>.
16. Muller K, Meineke V. Radiation-induced alterations in cytokine production by skin cells. *Exp Hematol* 2007; 35: 96–104.
17. Peter RU, Beetz A, Ried C et al. Increased expression of the epidermal growth factor receptor in human epidermal keratinocytes after exposure to ionizing radiation. *Radiat Res* 1993; 136: 65–70.
18. Segaert S, Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. *Ann Oncol* 2005; 16: 1425–1433.
19. Segaert S, Taberner J, Chosidow O et al. The management of skin reactions in cancer patients receiving epidermal growth factor receptor targeted therapies. *J Dtsch Dermatol Ges* 2005; 3: 599–606.
20. Erbitux. Summary of product characteristics 2006 <http://www.emea.europa.eu/humandocs/PDFs/EPAR/erbitux/H-558-PI-en.pdf>.
21. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. *Nat Rev Cancer* 2006; 6: 803–812.
22. Jost M, Kari C, Rodeck U. The EGF receptor—an essential regulator of multiple epidermal functions. *Eur J Dermatol* 2000; 10: 505–510.
23. Busam KJ, Capodice P, Motzer R et al. Cutaneous side-effects in cancer patients treated with the anti-epidermal growth factor receptor antibody C225. *Br J Dermatol* 2001; 144: 1169–1176.
24. Bonner JA, Risch KP, Trummel HQ et al. Enhanced apoptosis with combination C225/radiation treatment serves as the impetus for clinical investigation in head and neck cancers. *J Clin Oncol* 2000; 18: 47S–53S.
25. Huang SM, Harari PM. Modulation of radiation response after epidermal growth factor receptor blockade in squamous cell carcinomas: inhibition of damage repair, cell cycle kinetics, and tumor angiogenesis. *Clin Cancer Res* 2000; 6: 2166–2174.
26. Milas L, Mason K, Hunter N et al. In vivo enhancement of tumor radioresponse by C225 anti-epidermal growth factor receptor antibody. *Clin Cancer Res* 2000; 6: 701–708.
27. Bonner JA, Harari P, Giralt J et al. Duration of Mucositis and Dysphagia following radiotherapy (\pm Cetuximab) for Locoregionally Advanced Head and Neck Cancer. Multidisciplinary Head and Neck Cancer Symposium ASTRO, ASCO, and AHSN, January 18, Rancho Mirage, CA. Plenary Session 4 2007 97.
28. Campbell IR, Illingworth MH. Can patients wash during radiotherapy to the breast or chest wall? A randomized controlled trial. *Clin Oncol (R Coll Radiol)* 1992; 4: 78–82.
29. Roy I, Fortin A, Larochelle M. The impact of skin washing with water and soap during breast irradiation: a randomized study. *Radiother Oncol* 2001; 58: 333–339.
30. McQuestion M. Evidence-based skin care management in radiation therapy. *Semin Oncol Nurs* 2006; 22: 163–173.
31. Bolderston A, Lloyd NS, Wong RK et al. The prevention and management of acute skin reactions related to radiation therapy: a systematic review and practice guideline. *Support Care Cancer* 2006; 14: 802–817.
32. Aygenç E, Celikkanat S, Kaymakci M et al. Prophylactic effect of pentoxifylline on radiotherapy complications: a clinical study. *Otolaryngol Head Neck Surg* 2004; 130: 351–356.
33. Lin LC, Que J, Lin LK, Lin FC. Zinc supplementation to improve mucositis and dermatitis in patients after radiotherapy for head-and-neck cancers: a double-blind, randomized study. *Int J Radiat Oncol Biol Phys* 2006; 65: 745–750.
34. Perez-Soler R, Zou Y, Li T et al. Topical vitamin K3 (Vit K3, menadiolone) prevents erlotinib and cetuximab-induced EGFR inhibition in the skin. *J Clin Oncol* 2006; 24(18S) (Abstr 3036).