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Radiation-induced skin injury in the head and neck region: pathogenesis, clinics, prevention, treatment considerations and proposal for management algorithm

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ABSTRACT

Worldwide increase of head and neck cancers ranks these malignancies among top causes of cancer in human population. Radiation induced skin injury (RISI) is one of the major side effects of radiotherapy (RT). Skin of the neck is exposed to radiation due to necessity of therapeutic or prophylactic (elective) irradiation of neck lymph nodes and target organs, including the larynx and hypopharynx. The location of the neck exposes these regions of the skin to various additional exposomes such as ultraviolet radiation (UVR), pollution and cigarette smoke. There are many controversies or inconsistencies regarding RISI, from molecular aspects and therapy to terminology. There is lack of high-quality and large-sample studies in both forms of RISI: acute (aRISI) and chronic (cRISI). Finally, no gold standards in the management of aRISI and cRISI have been established yet. In this article, the authors discuss the pathogenesis, clinical picture, prevention and clinical interventions and present a proposed treatment algorithm.

Key words: radiotherapy side effects; radiation induced skin injury; radiodermatitis

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Introduction

Head and neck cancers are one of the most common malignancies in the world and their global burden is increasing [1]. For many years, radiotherapy (RT) has had an established position in the treatment of head and neck cancers, especially as an adjuvant treatment. However, despite significant progress in oncological RT, complication in the form of radiation-induced skin injury (RISI), also known as radiation dermatitis or radiodermatitis, continue to represent a serious, nearly unavoidable problem. There are many controversies or inconsistencies regarding RISI, from molec-

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ular aspects and therapy to terminology [2, 3]. However, it is recognized as the most common side effect of RT [4]. Moreover, the risk of RISI appears to be higher and the severity is greater in patients with head and neck cancers, reaching as high as 100%, while it is observed in lower rate in patients with other neoplasms [5]. One explanation is that skin at the neck area is exposed to various exposomes, such as ultraviolet radiation (UVR), pollution, cigarette smoke, which are well known factors that disrupt the function of the skin barrier [6], while other locations are protected from everyday direct exposure. It should also be noted that there are two forms of RISI: acute (aRISI) and chronic (cRISI). The former occurs during treatment (approximately 2–3 weeks following the initial irradiation), and the latter months (at least 90 days) or even years after RT [7–9]. Both forms of RISI can significantly reduce patient's quality of life, but more dangerously, an acute reaction can result in at least temporary discontinuation of treatment reducing effectiveness of RT [10–12].

Radiotherapy of head and neck cancers

RT is one of the mainstays of multidisciplinary treatment of head and neck cancers, together with surgery and systemic treatment. It can be used alone or in combination with chemotherapy and has an important role for every stage of head and neck cancer treatment - ranging from definitive and adjuvant treatment to palliative setting. Definitive RT is used in early stages of head and neck cancers, including oropharyngeal cancer [13], and is the primary treatment of nasopharyngeal cancer [14]. In adjuvant setting, for more advanced tumors, RT or chemoradiation enables eradication of residual microscopic spread of cancer in tumor bed and regional lymph nodes, which allows for decreasing risk of local and regional failure and prolongs progression free survival and overall survival after surgery [15–17]. For patients who are not eligible for surgery, RT or concomitant chemoradiation is the main method of treatment for both definitive [18] or palliative purposes. In a palliative setting RT eliminates or diminishes pain caused by tumor, as well as bleeding, obstruction of upper airways and digestive tract, thus improving quality of life of patients.

Immune and molecular signaling in radiation induced skin injury

The precise cellular and molecular mechanisms underlying acute and chronic RISI have not yet been completely elucidated [3]. Exposure of skin cells to radiation results in various cell death processes, including necrosis, necroptosis, apoptosis, autophagy, and accelerated senescence, as well as signaling pathways [19]. It is known that RT may induce DNA damage leading to cell-cycle arrest and cell death. DNA damage is probably a major triggering mechanism in the development of RT toxicity [20]. Additionally, the release of cytokines is thought to initiate biological responses in multiple cell types, causing late toxicity progression [21].

The heterogeneous occurrence and different degrees of RISI in individuals suggest that genetic variation may play a significant role in RISI development. The possible link of DNA modification affecting the sensitivity to RT involves the single-nucleotide polymorphisms (SNPs) as a response to RT. Thus, SNPs may function as a prognostic biomarker concerning the frequency and intensity of RISI [22].

The occurrence of RISI is partly related to individual radiosensitivity, especially the ability of DNA damage repair [23, 24]. The principal genome defense pathway to repair the radiation-induced DNA single-strand break is base excision repair (BER) associated with the following enzymes: DNA glycosylase, AP endonuclease, DNA polymerase, and DNA ligase [25]. Significant genes for the BER pathway, which are associated with human tumor susceptibility and radiation toxicity, involved: the X-ray repair cross-complementing 1 (*XRCC1*), 8-oxoguanine DNA glycosylase (*OGG1*), and apurinic/apyrimidinic endonuclease 1 (*APEX1*) genes [26].

It is suggested that the mutation in BER may be linked to acute and chronic RISI in cancer patients through reduced DNA repair ability. The association between SNPs of BER pathway genes and radiation reaction were mainly concentrated in breast, prostate, and lung cancers [26]. However, there are limited data concerning this problem in head and neck cancers. Pratesi et al. [27] demonstrated that the development of grade ≥ 2 mucositis was increased in head and neck squamous cell carcinoma patients with *XRCC1* rs25487 A allele. Alsbeih

et al. [28] found that *XRCC1* g.28152A allele was significantly associated with a lower grade condition of grade ≥ 2 skin and deep tissue fibrosis in nasopharyngeal carcinoma [28]. Another data with nasopharyngeal carcinoma indicated that the *XRCC1* rs25487 GA genotype was significantly associated with developing grade 3 dermatitis [29]. Furthermore, Chen et al. [20] detected the SNP of the *XRCC1* codon 399 in nasopharyngeal carcinoma patients, suggesting that it could be an essential predicting factor in the risk of aRISI during RT.

Wang et al. [26] examined a total of 5 SNPs in 3 BER pathway genes, including *XRCC1* (rs25487, rs25489, and rs3213245), *OGG1* (rs1052133), and *APEX1* (rs1130409) in nasopharyngeal carcinoma. Interestingly, these researchers found no association between the BER gene polymorphisms and radiotoxicity in tested patients [26]. As these authors noticed, this may be because the normal skin radiation damage depends mainly on cell regeneration, proliferation, and inflammation, while the role of DNA damage repair is relatively small.

Other genome-wide studies of SNP associated with RT toxicity indicated several candidate genes involved in DNA damage recognition and repair (e.g., *ATM, BRCA1, BRCA2*, and *TP53*), free radical scavenging (e.g., *SOD2*), and anti-inflammatory response (e.g., *TGFB1*) [21].

Literature data indicate that RT generates excessive levels of reactive oxygen species (ROS), disrupting redox homeostasis and leading to oxidative stress that can result in cell death. However, the tumor cell microenvironment is dynamic and responds to RT by activating numerous cellular signaling pathways [30]. Oxidative stress is responsible for activating signaling pathways, such as nuclear factor erythroid 2-related factor 2-antioxidant response element (Nrf2-ARE), which play an essential role in the inactivation consequence of this stress. Thus, activation of Nrf2 covers dissociation from inhibitor protein Keap1 and translocation of Nrf2 from the cytosol to the nucleus and, subsequently, binds to antioxidant response elements (ARE) located in the promoter region of genes that encode antioxidant (such as superoxide dismutase — SOD) and detoxifying enzymes [31]. SODs can pass through the dermal mucous membrane and perform an essential function as free-radical scavengers. SODs eliminate free radicals in the partial derma and enhance the skin and mucous membrane's tolerance dose to relieve or avoid a RISI [32].

Based on currently available data, exposure of cells to ionizing radiation and other toxic stresses leads to the simultaneous activation of multiple MAPK (Mitogen-Activated Protein Kinase) pathways. These signals play crucial roles in controlling cell survival and repopulation effects following irradiation [33]. MAPK, is an enzyme family, consisting of three types: extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 kinase, which are involved in cell proliferation, differentiation, apoptosis, and inflammation. The MAPK pathways also regulate the transcription factor activating protein 1 (AP-1), a heterodimer comprised of c-Fos and c-Jun, which, in turn, up-regulates matrix metalloproteinases (MMPs) in the skin [33, 34]. Moreover, recent data confirm that activation of MAPK promoted the degradation of Keap1 depending on p62, enabling Nrf2 to dissociate and transfer into the nucleus. Through the inhibition of Nrf2 and MAPK pathways, cell senescence can be alleviated, and radiation-induced ulcers may be prevented [35]. Preclinical studies demonstrated that the best-known triterpenoid, bardoxolone methyl (2-cyano3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) methylester/CDDO-Me/RTA 402/ is classified as an oral "antioxidant inflammation modulator" and is the most promising compound for reducing or preventing a RISI [31].

During RT, ROS can activate the other signaling pathway: nuclear factor kappa B (NF-κB), which plays a crucial role in the inflammatory process, immunity, cellular survival, and inhibition of apoptosis. NF-κB is a heterodimeric molecule of RelA (p65) and p50 subunits, which translocates into the nucleus and binds to the promoter region of target genes such as inter alia cyclooxygenase (COX-2) [36]. In response to radiation, NF-κB reduces cell death by promoting the expression of antiapoptotic proteins and activating the cellular antioxidant defense system. Moreover, constitutive activation of NF-κB-associated genes in tumor cells enhances radiation resistance, whereas deletion in vivo results in hypersensitivity to radiation [37].

It is suggested that radiation induces accelerated cellular senescence, also known as stress-induced premature senescence (SIPS), in the region of the stem cell population of the skin [19].

McCart et al. [19], analyzing the impact of RT on skin, demonstrated the upregulation of p21, one of major markers of senescence, in keratinocytes. Moreover, Iglesias-Bartolome et al. [38] observed that the inhibition of radiation-induced stem cell senescence reduced RISI in head and neck irradiation. The upregulation of the senescence-associated secretory phenotype (SASP), including interleukin (IL) -6 and IL-1, are expected outcomes of ionizing radiation-induced DNA damage, where dermal fibroblast and epidermal keratinocytes are identified as the primary sources of RT-induced IL-6 [3]. This study concluded that senescence-associated upregulation of IL-6, IL-1 signaling and IL-17 upregulation as well as CCR6+-mediated immune cell migration, are key elements of RISI. Thus, SIPS-related RISI is associated with the loss of tissue homeostasis leading to the dysregulation of a normal and timely repair process [3].

In order to fully understand the mechanism of radiation-induced skin fibrosis and the differences between RISI types, it is necessary to understand the signaling pathways controlling many vital processes. Several studies confirm that radiation-induced skin fibrosis are characterized by the deregulation of factors and cytokines such as TGF-β and Forkhead box O3 (FoxO3). FoxOs belong to a family of transcriptional regulators characterized by a conserved DNA-binding domain termed the forkhead box [39]. When FoxOs are located in the nucleus and bound to promoters that contain the FoxO consensus motif, they can act as transcriptional activators and repressors. In mammals, four FoxO isoforms have been identified: FoxO1, FoxO3, FoxO4, and FoxO6, wherein FoxO3 plays an essential role in various biological processes, including development, proliferation, apoptosis, metabolism, and differentiation, by regulating a broad spectrum of genes. Downregulation of FoxO3 through phosphatidylinositol 3-kinase (PI3K) could alleviate radiation-induced skin fibrosis [40]. Moreover, tissue damage repair and subsequent fibrosis involve multiple molecules and signaling pathways (e.g., transforming growth factor β (TGF-β), and Wnt/βcatenin) [40]. TGF-β is the primary factor of fibrosis. Radiation-induced TGF-β is expressed in skin tissue in a radiation dose–dependent manner. TGF-β is combined with its receptor to form a trimeric complex, causing tissue fibrosis. Activation of TGF-β1 can induce fibrosis via activation of both canonical (Smad-based) and non-canonical (non-Smad-based) signaling pathways. However, recent studies have indicated that the TGF-β/Smad pathway is an important/essential signaling pathway in skin fibrosis. Activated Smad protein translocates to the nucleus activating specific transcription, and triggering fibrosis in the nucleus. Moreover, activated TGF-β regulates fibrotic target genes by phosphorylating Smad2/Smad3 proteins. The TGF-β signaling pathway acts as a therapeutic target for radiation fibrosis [41].

Recent studies suggest that the effect of TGF-β on wound healing is mediated by β-catenin, and a similar process of Wnt/β-catenin signaling might contribute to radiation-induced fibrosis. The Wnt/βcatenin signaling pathway is vital to the physiological processes of early embryonic development, organ formation, and tissue regeneration in animals. Mutations in vital proteins in this signaling pathway can cause abnormal signal transduction, causing abnormal development or tissue regeneration [42]. Lee et al. [43] demonstrated that the radiation dose of 15 Gy to the dorsal skins of mice may not cause tissue contracture, although radiation-induced fibrosis may occur. In these experiments they used three groups of mice: those receiving phosphate-buffered saline (PBS), those receiving control adenovirus, and the third group receiving decoy Wnt receptor-expressing adenovirus (dE1-k35/sLRP6E1E2). During a 16-week observation period, the mice treated with sLRP6E1E2-expressing adenovirus showed a significant reduction in the excessive deposition of type I collagen. These findings provide compelling evidence that modulating the Wnt/β-catenin pathway has the capacity to mitigate the severity of radiation-induced dermal fibrosis.

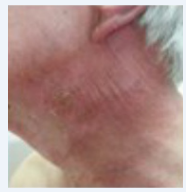
Therefore, further research using large cohorts, especially genome-wide associated studies, are necessary to determine if there is an association between the SNP and RT toxicity. This approach would provide a better dialogue between basic researchers and clinicians to develop novel treatments.

Clinical presentation

Acute radiation induced skin injury

aRISI is skin damage observed within 90 days after the first irradiation [8]. The changes to epi-

Table 1. Clinical scales dedicated to early post-radiation reactions

Grade	0	I	II	III	IV	V
						
NCI CTCAE v.5.0	No skin lesions	Faint erythema, dry desquamation	Moderate to brisk erythema, patchy moist desquamation that is confined to the skin folds and creases moderate edema	Moist desquamation in areas other than in the skin folds and creases, bleeding that is induced by a minor trauma or abrasion	Skin necrosis or ulceration of full thickness in the dermis, spontaneous bleeding from the involved site	Death
RTOG		Follicular, faint or dull erythema, epilation, dry desquamation, decreased sweating	Tender or brisk erythema, patchy moist desquamation that is confined to the skin folds, moderate edema	Confluent, moist desquamation in areas other than in the skin folds, pitting edema, bleeding may occur	Ulceration, hemorrhage and necrosis	Death

NCI — National Cancer Institute; CTCAE — Common Terminology Criteria for Adverse Events; RTOG — Radiation Therapy Oncology Group

dermis integrity with increase transepidermal water loss (TEWL), especially with subsequent RT sessions and accumulation of dose, lead to a wide variety of symptoms including erythema, xerosis, desquamation, hyperpigmentation and other subjective symptoms [8, 9, 44].

The first symptom of aRISI is erythema which occurs around 10 to 14 days after RT in patients receiving doses between 6 and 20 Gy. Erythematous lesions are usually accompanied by skin oedema and fragility. The patient may feel discomfort in the form of increased skin tension and/or accompanying itching or burning sensation or in some cases pain. Additionally, the loss of sebaceous glands leads to skin dryness. As a compensation to skin damage, after 3–4 weeks of radiation, the increased mitotic activity leads to improper formation of new cells, which manifests as a desquamation, typically observed in doses higher than 20 Gy. Doses above 30 Gy exceed the repair capacity of the epidermis that may provoke its detachment with possible blisters formation, which is called moist desquamation. The impaired skin barrier function predisposes also to skin infections, mostly bacterial one. In severe reactions ulceration and even necrosis of the irradiated tissue may also be present. Depending on the location, mucositis and hair loss can be observed. Yet, most cases of aRISI are self-limiting and resolve within 2–4 weeks following the end of treatment [8, 9].

According to the National Cancer Institute (NCI) of the National Institutes of Health (NIH) standardized definitions for adverse events (AEs), known as the Common Terminology Criteria for Adverse Events (CTCAE, also called "common toxicity criteria" [CTC]), the severity of skin toxicity for patients under RT can be classified into 5 grades (Tab. 1). The five-graded scale was proposed also by the Radiation Therapy Oncology Group (RTOG) (Tab. 1) [45, 46]. Grade 1 toxicity, which affects approximately 90% of patients, remains the major concern, while grade 2 is observed in 30% [9].

Chronic radiation induced skin injury

cRISI can appear from months (the earliest changes appear 90 days after cessation of RT) to as long as 20 or 30 years after treatment. The changes may persist or develop de novo after resolution of the acute phase. Unlike aRISI, late toxicity is a persistent and, in many cases, progressive complication. It encompasses various morphologies and may manifest itself with subjective symptoms (such as hypersensitivity and/or pruritus), vascular changes (telangiectasia), dermis atrophy and fragility, pigmentation changes (poikiloderma), and cicatrical alopecia. While delayed necrosis is rarely observed, it mostly affects the nose, ears or scalp. Radiation-induced fibrosis can cause skin thickening, lymphedema and reduced range of motion [8, 9, 46]. It should be noted that higher

Table 2. The Late Effects Normal Tissue Task Force-Subjective, Objective, Management and Analytic (LENT-SOMA) scale dedicated to late post-radiation reactions (quoted for Mao 2017)

Grade	I	II	III	IV
Features				
Subjective	Hypersensitivity/pruritus	Intermittent pain	Persistent pain	Debilitating dysfunction
Scaliness/roughness	Present and asymptomatic	Symptomatic	Requires constant attention	
Edema	Present and asymptomatic	Symptomatic	Secondary dysfunction	Total dysfunction
Alopecia	Thinning	Patchy and permanent	Total and permanent	
Pigmentation change	Transitory	Permanent		
Erosion/ulcer necrosis	Epidermal	Dermal	Subcutaneous	Bone exposed
Telangiectasia	Minor	Moderate	Severe	
Fibrosis	Present and asymptomatic	Symptomatic	Secondary dysfunction	Debilitating dysfunction
Atrophy	Present and asymptomatic	Symptomatic	Secondary dysfunction	Debilitating dysfunction

grades of aRISI are associated with higher grades of chronic skin injury, including fibrosis [47].

The Late Effects Normal Tissue Task Force-Subjective, Objective, Management and Analytic (LENT-SOMA), RTOG and Dische scoring systems can be used to assess toxicity and skin damage in cRISI. The LENT-SOMA scale is the most frequently used and recommended (Tab. 2) [48–50].

Importantly, various risk factors can influence the development of RISI. They can be categorized as treatment related and/or patient related [9, 46, 51] and are presented in Table 3.

Table 3. Risk factors of acute radiation induced skin injury (RISI) [according to 9, 46, 51, 57, 62, 67, 68, 97, 98]

Risk factors of RISI	
Treatment related	**Patient-related**
Total dose delivered to the skin	Individual patient radiosensitivity
Volume of skin irradiated	The degree of sun exposure
Dose schedule	Smoking status
Radiotherapy technique	Nutritional status/overweight (BMI)
Quality of radiotherapy	Comorbidities e.g. diabetes
Concomitant chemotherapy/molecular treatment	Tissue volume

Management

Unfortunately, despite many possible interventions described in the literature, significant discrepancies in clinical practice exist and there are no widely accepted recommendations regarding the management of the skin of patients undergoing RT [7, 46, 52–54]. Recently, comparison of the available clinical practice guidelines was proposed by Finkelstein et al. [46]. In general, there are two main elements of RISI's management: prevention and treatment.

Acute radiation induced skin injury

Prevention

Treatment-related prevention

The priority in prevention of aRISI at the stage of RT planning is to balance protection of all healthy organs and tissues, including skin, and delivering full therapeutic/prophylactic dose for tumor and lymph nodes. In terms of treatment planning the following parameters were identified to

correlate with the grade of aRISI: volume of skin irradiated, total dose delivered to the skin, dose schedule, RT technique, quality of RT including adaptive RT, as well as concomitant chemotherapy and/or molecular treatment.

Volume of skin irradiated as well as total dose delivered depend on advancement of disease. For bulky (> 3 cm in largest diameter) metastatic lymph nodes, definitive RT results in the need of delivering higher dose of irradiation to larger volumes, including skin volume. However, there are no experimentally defined levels of doses and volumes correlating with the risk of high grades of aRISI, while such dose-volume correlations have been established for late effects of RT [55]. Recently, Kawamura et al. [56] designed and tested a scoring system for patients irradiated for head and neck cancer, based on dosimetric and clinical parameters, evaluating the risk of incidence of grade 3 aRISI. The most important dosimetric parameter was volume of skin irradiated to the dose of 60Gy or higher (V60Gy), where 43.4% incidence of grade 3 aRISI correlated with skin volume greater than 38cm3 receiving V60Gy [56, 57].

While the impact of dose per fraction on aRISI in head and neck cancer patients is still not well documented, it is known from breast cancer RT studies that doses higher than 2 Gy per fraction induce less dermatitis with higher grade than conventional 2 Gy doses. However, higher doses per fraction, i.e. 3–4 Gy, are used mostly in palliative, short schedules of RT in head and neck cancer patients, thus observation from breast postoperative RT cannot be extrapolated to patients with head and neck cancer treated with definitive RT [58, 59]. Also, there is no sufficient evidence for aRISI in stereotactic RT so far, while its use in head and neck is still a subject of debate [60].

Yet, Intensity Modulated Radiation Therapy (IMRT) is the most often used technique of head and neck irradiation. It's highly conformal way to deliver homogenous dose directly to the tumor and to spare healthy organs and tissues. The optimal treatment plan is achieved by "sculpting" the dose in the target region, which allows to minimize the dose in the skin region. However, results of comparison of IMRT and less conformal methods, i.e. Three-Dimensional Conformal RT (3D CRT), are conflicting. The reason of those discrepancies and observed higher risk of grade 3 aRISI with highly conformal techniques might lie in differences between RT departments in defining a planning target volume (PTV), especially those close to the skin surface as well as in the use of bolus [61]. Another risk factor for grade 3 and 4 aRISI might be altered fractionation. RTOG 9003 study reported 11% of grade 3 and 4 acute dermatitis with hyperfractionation and accelerated fractionation in comparison with standard schedule of RT (7% of grade 3 and 4 acute dermatitis) [62].

The next step in improving conformality of dose delivered is use of protons instead of photons for irradiation of selected head and neck cancer patients. Protons are most often used for patients with nasopharyngeal cancer, where sparing of the brain stem or optic nerves is of the highest priority. It is expected that due to deep dose distribution of protons the skin will be also better protected from aRISI. However, there is no available data to clearly demonstrate difference between protons and photons IMRT with regards to aRISI in head and neck cancer patients. [63].

Prevention of aRISI starts at the stage of treatment planning. However, efforts to minimize the dose delivered to the skin without jeopardizing the dose to the tumor continue during the whole RT treatment. Accurate delivery of a precise treatment plan requires verification prior to each fraction. Daily imaging of irradiated region is mandatory and allows the RT team to observe changes in both tumor size and patients' anatomy. It is especially important when patients lose weight as a consequence of acute throat and/or oral mucositis and difficulties in eating and swallowing. Weight loss results in decreasing the distance between skin and irradiated lymph nodes shifting the high dose region towards the skin. Preparation of a new treatment plan is mandatory in such a situation to better protect the skin from unintended dose increase. Results of studies investigating the role of adaptive radiotherapy in decreasing risk of aRISI have been inconclusive so far [64]. However, adaptive radiotherapy is a state of art approach in head and neck irradiation as prevention of increased risk of delivering higher than planned dose to the skin, which can result in higher grades of aRISI [65, 66].

Patients treated with concomitant chemoradiation are at higher risk of grade 3 and 4 aRISI.

In head and neck cancer cisplatin and cetuximab are most often used concomitantly with radiation. Cisplatin is a well-known radiosensitizer, which, among others, inhibits repair of DNA damages caused by radiation. Concomitant treatment increases grade 3 and 4 acute side effects of radiation, including dermatitis [57, 67]. Another drug extensively tested in concomitant setting is cetuximab. Cetuximab is a recombinant chimeric IgG1 monoclonal antibody against the ligand binding domain of EGFR. It enhances radiation response in many ways, including inhibiting DNA repair by binding and blocking EGFR [68]. Blocking the EGFR signaling pathway has an impact not only on cancer cells but also on skin components, immune response and migration of skin cells enhancing intensity of aRISI caused by radiation [69]. According to EORTC survey, grade 3 and/or 4 radiation dermatitis is observed in 49% of head and neck cancer patients treated with cetuximab and concurrent RT [70]. There are also no specific treatment related methods of prevention of aRISI caused by concurrent drugs.

Skin care-related prevention

Different forms of skin cleansing are recommended upon RT. For example, according to MASCC guideline washing with water with or without mild soaps or shampoos is strongly recommended [7, 53]. Oncology Nursing Society (ONS), on the other hand, strongly recommends the use of soap and water [52]. Washing with water alone seems inappropriate because most of the contaminants on the skin is insoluble in water. More importantly, according to our current understanding of skin physiology, water can compromise the skin barrier due to the washing away of the skin's natural moisturizing factor [71, 72]. This may be of particular importance during RT as signs and symptoms of a compromised epidermal barrier have previously been described in irradiated patients, even in cases without clinically obvious aRISI [73]. It is well known that a disrupted skin barrier can lead to inflammation [6]. Currently, for washing both healthy and diseased skin, it is recommended that soap-free cleaning agents with synthetic detergents and an appropriate pH (so-called "syndets") are used rather than classic soap. The high-pH cleansing products can further degrade the skin barrier by disrupting lipid bilayers and affecting the microbiome. In addition, a high-quality product should contain moisturizers (to reduce TEWL and improve hydration) and omit unnecessary ingredients such as fragrances and dyes [71, 72]. A short bath or shower in lukewarm water is recommended to avoid dehydration of the epidermis [74, 75] and hand washing instead of a sponge to avoid potential microtrauma and/or superinfection. To sum up, it was proven that washing the skin with or without soap during RT resulted in less severe RISI and less frequent moist desquamation while reducing the risk of secondary infection; [76, 77] however, in our opinion, cleansing the skin with water and syndet instead of soap is a better way to cleanse and protect the skin upon RT. Washing the hair is not expected to affect sensitivity to RT [78], although it seems advisable to recommend fragrance-free shampoos for sensitive skin.

It should be noted, that cleansing without the use of emollients may exacerbate xerosis and inflammation of the skin [72]. SCoR recommend using moisturizers on intact skin [46]. For decades, emollients have been a cornerstone element of the basic therapy in atopic dermatitis — a flagship example of dermatosis associated with skin-barrier defect [75]. However, they are recommended in many other skin conditions including skin dryness as well as in RISI [9, 79]. Emollients provide a temporary restoration of the impaired barrier function by reducing TEWL, relieving itching, reducing inflammation and acting as a steroid-sparing agents [75, 79]. By definition, they contain at least humectant (i.e. urea, glycerol, isopropyl myristate) and occludent (i.e. petrolatum). Other ingredients that can be incorporated into emollients include: physiological lipids such as ceramides, cholesterol and free fatty acids (note: the right ratio between them should be maintained, which means approx. a 3:1:1 molar ratio), protein-free oat plantlet extracts or bacterial lysates which influence the skin microbiome [75, 80]. The latter seem to be of particular interest in the context of RISI, as recent research has shown significantly reduced bacterial diversity in comparison to controls [81]. Given our contemporary understanding of the role of skin-colonizing microbiota in maintaining normal skin barrier

functions, it seems that effort should be focused on maintaining/restoring a normal microbiome through appropriate skin care [82]. And even if an association of *Staphylococcus* (*S.*) *aureus* colonization with the severity of acute radiation dermatitis is observed [83], it is important to bear in mind that secondary infection is a common complication, not the cause, of various forms of skin inflammation, especially those with accompanying exudate [84]. The frequency of *S. aureus* colonization among patients with atopic dermatitis ranges from 40–80% and correlates with the severity of the disease. It is effectively reduced by topical corticosteroids and calcineurin inhibitors, and there is no need to use topical/systemic antibiotics unless clinical signs of infection are present [75]. However, it should be noted that recently Kost et al., in their randomized, controlled study (including 123 patients) indicated a beneficial effect of bacterial decolonization from the nose and skin on the risk of RISI [85]. In this study, chlorhexidine was used as an antiseptic, which is widely considered to damage the skin barrier and potentially cause allergies [86]. For patients with atopic dermatitis and recurrent skin infections, baths with sodium hypochlorite 0.005% are recommended, recognized as the least aggressive antiseptic [75, 87].

There are also some studies that claim the usefulness of skin care products containing Chamomilla in preventing/treatment of RISI [88, 89]. It should be emphasized, however, that chamomile plant extracts contain a number of ingredients, including anti-inflammatory agents (i.e. bisabolol), but also potential sensitizers (i.e. tonghaosu) and there are many reports of allergic reactions to topical products containing chamomile [90]. Emulsifiers, fragrances and preservatives should be avoided as they are the main causes of contact allergy. It should be noted that the aqueous creams listed in the various recommendations naturally contain higher concentrations of emulsifiers. On the other hand, some authors claim that the oil phase of dermocosmetics may block the penetration of the RT beam; therefore, they propose the use of gels [91]. However, it should be emphasized that gels as well as pure oils can exacerbate dryness [75, 92]. Hence, emollients with rationally selected ingredients seem to be the best option for RISI. Ideally, topical emollients should be applied every time directly after bath or shower following gentle drying (patting dry avoiding rubbing) when the skin is slightly humid (so called soak and smear rule), and the total number of emollient applications per day (with or without prior skin cleansing) should be at least two [75, 79]. Importantly, the emollient should be applied at least 1 hour before the RT session, otherwise an increased dose of radiation will be delivered to the epidermis [9].

The patient should also be instructed on the principles of photoprotection [9]. These include: (1) use sunscreen with a sun protection factor (SPF) of 50+ and UVA protection; (2) use the product all year round, regardless of the weather (as exposure to UVA rays does not vary much depending on the season and cloud cover); (3) multiple applications per day; (4) use an appropriate amount of product, e.g. apply about 5 ml of sunscreen to cover the head and neck area [93]. Extreme temperatures should also be avoided [91].

Electric razors and loos, soft clothing are recommended to reduce the risk of skin injuries in the treatment area [91]. Currently, the use of deodorants/antiperspirants is widely accepted as they do not increase the risk of RISI [46, 52, 91, 94], however, alcohol-based products, i.e. perfumes, should be avoided.

Prophylactic use of non-absorbing film forming dressing, topical glucocorticosteroids, silver sulfadiazine as well as semipermeable dressings is suggested by some guidelines but with varying degrees of recommendation [46, 52, 53, 95]. Rosenthal et al. [96] suggest the use of topical glucocorticosteroids, such as mometasone furoate, twice a day from the first day of RT until 2 weeks following the end of RT. However, prolonged use of topical glucocorticosteroids can lead to thinning of the skin and the appearance of telangiectasias. Therefore, the proactive therapy regimens proposed for atopic dermatitis may be worth considering. Currently, in asymptomatic atopic dermatitis, topical application of calcineurin inhibitors (tacrolimus, pimecrolimus) once daily twice weekly (e.g. Monday and Friday) is recommended to reduce subclinical inflammation [75]. However, it should be emphasized that no studies on the prophylactic use of topical calcineurin inhibitors in RISI have been published so far. Therefore, their

inclusion should be considered very cautiously. Alternatively, low- to medium-potency topical glucocorticosteroids may be used instead of topical calcineurin inhibitors. When topical glucocorticoids are used in proactive therapy, a weekend regimen is sometimes proposed (once a day on Saturday and Sunday).

Other forms of prevention

Body mass index > 25 is considered an independent predictor of severe aRISI, however, weight loss during RT is an independent predictor of cRISI [97]. On the other hand, there is a higher likelihood of cRISI development among patients with elevated BMI. A relationship between smoking and the risk of RISI was also demonstrated [51, 98]. The significance of both factors in the development of RISI does not seem surprising, as both are well-understood skin barrier disruptors [99, 100].

In conclusion, we believe that regular, daily care with syndets, emollients and sunscreens, together with smoking cessation and careful BMI control can reduce the risk of aRISI and should be considered as basic therapy in all patients undergoing RT. In patients at high risk of developing RISI (Tab. 3), proactive therapy with low- or medium-potency topical glucocorticosteroids may be considered.

Treatment

There are many therapeutic strategies suggested to be useful for RISI, ranging from topically applied products (often containing plant-derived substances), to topical glucocorticosteroids and hydrogel dressings, to experimental therapies such as hyperbaric oxygen therapy and mesenchymal stem cells [96].

Proper skin care should be continued [46], however, direct application of emollients to inflamed skin may cause skin stinging/burning [75]. In such a situation, it is suggested to use solely anti-inflammatory therapy for the first few days with temporary discontinuation of emollients.

Potent and very potent topical glucocorticosteroids (i.e. mometasone furoate and betamethasone 17-valerate respectively) remain the mainstay of RISI therapy. They are recommended to alleviate symptoms of grade 1 aRISI, such as erythema, pruritus, and dry desquamation, and reduce the risk of grade 2 and 3 of aRISI [46, 53, 96]. However, as mentioned above, their prolonged use can lead to thinning of the skin and the appearance of telangiectasias. Topical calcineurin inhibitors are used as an alternative to topical glucocorticosteroids in many dermatological indications. Unfortunately, there is only one study in the available literature on the use of calcineurin inhibitors in the management of radiation-induced injury. Rajaganapathy et al. [101] demonstrated that intravesical liposomal tacrolimus protects against radiation cystitis in a rat model. When discussing topical calcineurin inhibitors in the context of RT, it should be emphasized that topical calcineurin inhibitors (contrary to topical corticosteroids) lead to an improvement of the skin barrier condition in patients with atopic dermatitis [102, 103]. Additionally, we do not currently believe that these group of drugs increase the risk of developing non-melanoma skin cancers [104, 105]. Therefore, topical calcineurin inhibitors may bring potential benefits; however, further research is needed before they can be recommended.

There is no consensus concerning the use of hydrogels and dressings, however, some authors and guidelines suggest usefulness of the use of hydrogels as well as hydrocolloid, silicon-based and moisture-retentive dressings to reduce moist desquamation or treat ulceration [46, 53, 95, 106]. The advantage of dressings is the creation of a stable, moist environment that enables faster re-epithelialization. The selection of the dressing should be based primarily on exudate level and be consistent with the T.I.M.E. protocol (tissue management, infection/inflammation control, moisture balance, promotion of epithelialisation) commonly accepted in wound treatment [95, 107].

In case of superinfection, the use of silver sulfadiazine or topical/oral antibiotics is suggested, but with varying degrees of recommendation [46, 53]. It should be noted, that there are many conflicting opinions in the literature regarding the usefulness of silver sulfadiazine in the treatment of wounds and ulcerations. Currently, it is recommended for use no longer than 14 days (as it slows down re-epithelization) and it is not recommended for prophylaxis [108,109]. In cases of critically colonized wounds or wounds at risk of infection, polyhexanide is preferred over silver sulfadiazine [109]. Finally, some dressings also have antimicrobial properties [95].

Oral analgesics can be given for pain [46]. However, when considering topical analgesics, their potential to induce phototoxic reactions should be borne in mind [110]. The following topically applied nonsteroidal anti-inflammatory drugs have phototoxic potential: arylpropionic acid analogs (e.g. ibuprofen, ketoprofen, naproxen), pyrazolidinedione derivatives (e.g. phenylbutazone) [110, 111].

The literature also mentions the potential usefulness of photobiomodulation therapy (PBMT). This method is used primarily in aesthetic medicine. The meta-analysis focused on the utility of PBMT in RISI discusses 5 publications, with 4 originating from a single center. In the analyzed studies, it is often emphasized that improvement was achieved but without statistical significance, or assuming that a significant difference was reached at $p = 0.05$. In 2 out of 5 studies, the authors do not find evidence of the method's effectiveness. No adverse effects other than RISI are discussed in any of the studies [112].

The oral enzyme mixture also appears in the MASCC recommendations [53]. However, the only study meeting RCT standards did not confirm the product's effectiveness [113].

The negative recommendations include gentian violet, paraffin, or petroleum-based dressing use [46, 53], aloe vera [46, 53, 94, 114], trolamine [96, 115], calendula, emu oil [94], chamomile, ascorbic acid, pantothenic acid, sucralfate [96]. There are also several other agents (e.g., hyaluronic acid, epidermal growth factor, granulocyte and macrophage colony-stimulating factor) that may be potentially useful, but further studies are needed before a recommendation can be made [96]. It is worth noting that in many cases creams containing specific additional substances not only fail to deliver a better effect than standard emollients, but are also often more expensive.

It seems reasonable to use the "step-up approach" when selecting the treatment option. According to this method, the treatment option should be chosen based on the signs/severity of RISI. In grade 1 aRISI the usefulness of topical glucocorticosteroids in alleviating symptoms is suggested, in grade 2 or 3 properly selected dressings are recommended. ISNCC recommends to use topical betamethasone 17-valerate and mometasone furoate even in high-grade aRISI [46]. In the case of infection, silver sulfadiazine, topical and / or oral antibiotics are recommended [46, 53]. Figure 1 presents the proposed step-by-step procedure for patients undergoing RT.

Chronic radiation induced skin injury

Unfortunately, there is much less to offer to cRISI patients. Last year, a consensus on the management of cRISI was proposed [116]. Of the 63 questions or statements, strong consensus was reached only for 15, while for 32 statements no consensus was reached. It was agreed that the proper skin care (including sunscreen) should be continued. Pulsed dye laser and/or intense pulsed light are recommended to reduce persistent erythema and telangiectasia, and Q-switched laser may be considered for hyperpigmentation [9, 46, 116]. In the case of fibrosis and contractures physiotherapy, autologous fat grafting and fractional ablative laser therapy may be considered [116, 117]. Additionally, some experts suggest the use of oral pentoxifylline and vitamin E in combination with physical therapy [116], while ulcers should be treated with properly selected dressings in accordance with the T.I.M.E. protocol [95]. Importantly, RT also increases the risk of non-melanoma skin cancers (NMSCs) in the irradiated area [118–121]; therefore, although NMSCs are not part of the RISI picture, it seems reasonable to recommend a dermatological assessment with obligatory dermoscopy at least once a year.

Conclusions

Unfortunately, despite our extensive knowledge of the mechanisms underlying RISI and the many possible therapeutic interventions described in the literature, we still do not have universally accepted recommendations for skin management during RT. More well-designed studies are necessary to validate current recommendations. It seems, however, that proper skin care (including regular, daily care with syndets, emollients, sunscreens, smoking cessation etc.) as well as topical glucocorticosteroids and dressings matched to the degree of exudate are currently the standard of care during RT. Additionally, it is worth emphasizing the need for annual dermatological check-ups for possible early detection of skin cancer for all patients after completed RT treatment.

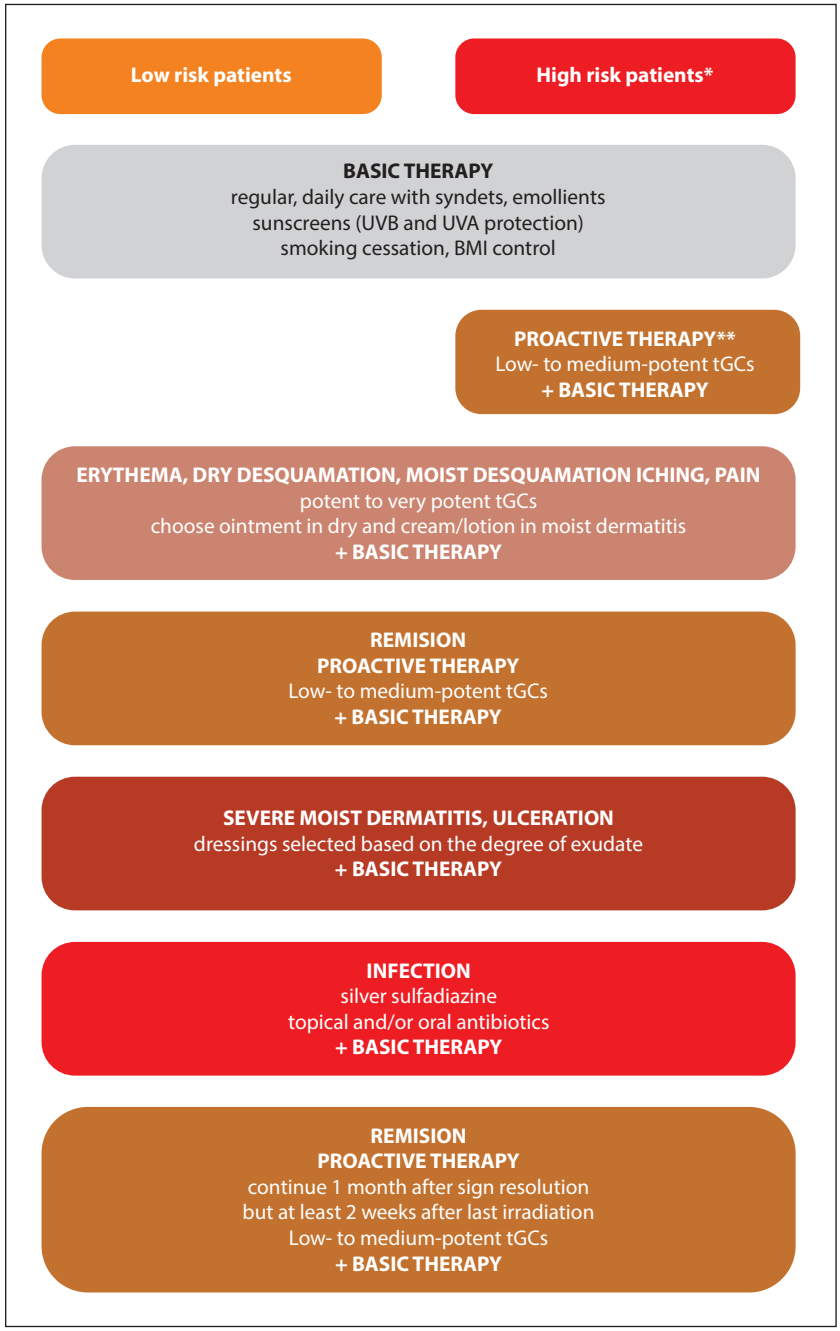


Figure 1. "Step-up approach" for the prevention and treatment of acute radiation induced skin injury (aRISI). BMI — body mass index; tGCs — topical glucocorticosteroids; *according to Table 3; **explained in the text

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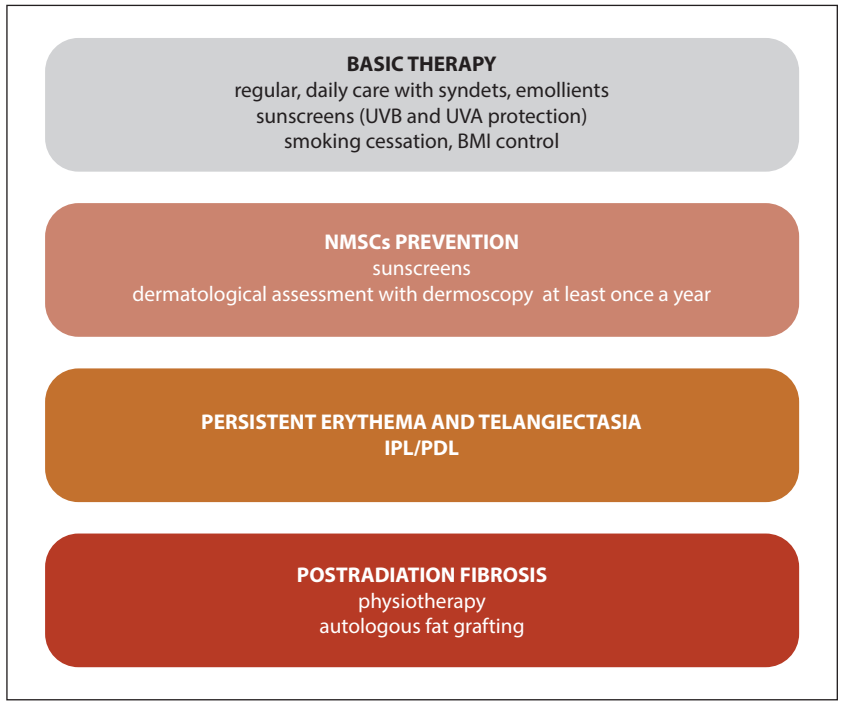

Figure 2. Management options for patients after RT and patients with chronic radiation induced skin injury (cRISI). BMI — body mass index; NMSCs — non-melanoma skin cancers; IPL — intensive-pulsed light; PDL — pulsed dye laser

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