

# Chronic radiation-induced dermatitis: challenges and solutions

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**Abstract:** Chronic radiation dermatitis is a late side effect of skin irradiation, which may deteriorate patients' quality of life. There is a lack of precise data about its incidence; however, several risk factors may predispose to the development of this condition. It includes radiotherapy dose, fractionation, technique, concurrent systemic therapy, comorbidities, and personal and genetic factors. Chronic radiation dermatitis is mostly caused by the imbalance of proinflammatory and profibrotic cytokines. Clinical manifestation includes changes in skin appearance, wounds, ulcerations, necrosis, fibrosis, and secondary cancers. The most severe complication of irradiation is extensive radiation-induced fibrosis (RIF). RIF can manifest in many ways, such as skin induration and retraction, lymphedema or restriction of joint motion. Diagnosis of chronic radiation dermatitis is usually made by clinical examination. In case of unclear clinical manifestation, a biopsy and histopathological examination are recommended to exclude secondary malignancy. The most effective prophylaxis of chronic radiation dermatitis is the use of proper radiation therapy techniques to avoid unnecessary irradiation of healthy skin. Treatment of chronic radiation dermatitis is demanding. The majority of the interventions are based only on clinical practice. Telangiectasia may be treated with pulse dye laser therapy. Chronic postirradiation wounds need special dressings. In case of necrosis or severe ulceration, surgical intervention may be considered. Management of RIF should be complex. Available methods are rehabilitative care, pharmacotherapy, hyperbaric oxygen therapy, and laser therapy. Future challenges include the assessment of late skin toxicity in modern irradiation techniques. Special attention should be paid on genomics and radiomics that allow scientists and clinicians to select patients who are at risk of the development of chronic radiation dermatitis. Novel treatment methods and clinical trials are strongly needed to provide more efficacious therapies.

**Keywords:** chronic radiation dermatitis, radiation-induced fibrosis, late skin toxicity, radiotherapy side effects

## Introduction

The rapid development of radiation oncology in recent years caused significant improvement of cancer treatment effectiveness. Irradiation is associated with a variety of side effects, which depend on several factors, for example, site of treatment, radiation dose, and technique. One of the visible and common manifestations of radiation toxicity are acute and chronic skin reactions, commonly described as "radiation dermatitis".<sup>1,2</sup> Originally, dermatitis is defined as "inflammation of the skin". However, in the literature data, the term "radiation dermatitis" covers a broader spectrum of symptoms and manifestations of postirradiation skin toxicity.<sup>3</sup> Acute skin toxicity usually develops within 90 days

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after the beginning of irradiation, whereas chronic radiation dermatitis may develop many years after treatment. The skin after radiotherapy may look healthy, but the occurrence of chronic postirradiation reaction may develop suddenly and with various severity.<sup>2</sup> Chronic radiation dermatitis is usually an irreversible and progressive condition, which may heavily deteriorate patients' quality of life.<sup>4</sup> This review presents a contemporary view on chronic radiation dermatitis and point out the challenges that ought to be taken up.

## Incidence and risk factors

### Incidence

There is no precise data on the incidence of chronic radiation dermatitis. In general, 95% patients who undergo radiotherapy develop some form of skin toxicity.<sup>1,5</sup> There is no direct connection between experiencing an acute skin reaction and further development of chronic radiation dermatitis.<sup>3</sup>

### Risk factors

Factors related to the higher incidence of chronic radiation dermatitis may be divided into two groups – directly dependent on irradiation and nondependent on irradiation. The factors increasing the risk of chronic radiation dermatitis dependent on radiotherapy include

- higher total irradiated volume;<sup>6,7</sup>
- higher total dose;<sup>6,7</sup>
- altered fractionation (single fraction, hypofractionation, hyperfractionation, sometimes data on altered fractionation schemes are conflicting);<sup>8,9</sup>
- radiotherapy technique without intensity modulation and large fields (two-dimensional [2D] radiotherapy, three-dimensional [3D]-conformal radiotherapy);<sup>10,11</sup>
- kind of radiotherapy (postoperative radiotherapy);<sup>12</sup>
- use of bolus, which increases dose received by skin.

There are also several factors not directly connected with radiotherapy modality, which include

- Concurrent chemotherapy – some agents may significantly increase the risk of late skin complications, but a clear correlation has not been yet established. Results of randomized clinical trial comparing sequential vs concurrent chemotherapy in irradiated breast cancer patients show a significantly higher risk of radiation-induced fibrosis (RIF) in concurrent chemotherapy group.<sup>13</sup>
- Concurrent targeted therapy – biological and/or targeted therapies are a novel approach in many malignancies. They are often combined with radiotherapy. Some

recently published reports show that this combination may lead to increased treatment toxicity manifested as severe skin complications. Known examples are BRAF inhibitors and epidermal growth factor receptor inhibitors.<sup>14–16</sup>

- Connective tissue disorders – there is a connection between a higher incidence of postirradiation skin toxicity and connective tissue disorders (such as systemic lupus erythematosus, scleroderma, and rheumatoid arthritis). The review of eight observational studies that included 404 patients with connective tissue diseases who were treated with radiotherapy showed that there was a statistically significant association with late radiation-induced complications in normal tissues (fibrosis, osteonecrosis, and bone fractures).<sup>17</sup>
- Skin disorders – although radiation therapy was used by dermatologists in the treatment of some skin disorders, such as acne, psoriasis, or atopic eczema, these conditions increase the risk of chronic radiation dermatitis.<sup>2</sup>
- Genetic factors – the response to radiation therapy may vary among patients, including both benefits and toxicity of treatment. Patients with DNA repair-deficiency disorders present symptoms of chronic radiation dermatitis.<sup>18</sup> Moreover, some genes responsible for increased risk of RIF have been already identified.<sup>19</sup>
- Personal factors – some of individual factors that may be both modifiable and nonmodifiable are connected with the higher risk of chronic radiation dermatitis. Female sex was identified as an independent predictor of severe late skin reaction.<sup>20</sup> The reaction on radiation is related to the healing ability of skin, which decreases with age. It is caused by aging of cell lines, thickening of epidermis, loss of collagen, and reduction in the capillary network.<sup>21</sup> Healing process of skin may be also disrupted by poor nutritional status, which affects ~50% of cancer patients.<sup>22</sup> In smokers, several mechanisms, such as impaired oxygenation and elevated carboxyhemoglobin levels, disturb the postirradiation skin recovery and may exacerbate acute and chronic skin reactions.<sup>21</sup> There is no clear connection between skin color and severity of skin reaction; however, it is thought that individuals with fair or pale skin suffer from more severe skin toxicity.<sup>21</sup> Another considerable risk factors of chronic radiation dermatitis are obesity, chronic sun exposure, and ethnicity.<sup>2,5,23</sup>

## Pathophysiology

Available data suggest that chronic radiation dermatitis is caused by imbalance of proinflammatory and profibrotic cytokines, which starts after irradiation and lasts for months

or even many years. These include tumor necrosis factor-alpha (TNF-alpha), interleukins 6 and 1 (IL-6 and IL-1), tumor growth factor beta (TGF-beta), platelet-derived growth factor (PDGF), and connective tissue growth factor.<sup>24-28</sup>

TNF-alpha, IL-6, and IL-1 are responsible for persistent inflammation, whereas TGF-beta and PDGF promote fibrosis by activating fibroblasts and inducing synthesis of extracellular matrix proteins and matrix metalloproteinases.<sup>24-26,29,30</sup>

The concomitant radiation-induced endothelium damage results in improper vascularization of irradiated skin and restricts blood perfusion. It may exacerbate the fibrosis and deteriorate healing process.<sup>31</sup> This phenomenon, together with secretion of PDGF, can also play a role in pathogenesis of telangiectasia.<sup>32</sup>

In addition, persistent inflammation and secretion of proinflammatory cytokines lead to leukocyte infiltration, which may cause other manifestations of chronic radiation dermatitis, such as skin atrophy or necrosis.<sup>33</sup>

## Clinical manifestations

Chronic postirradiation skin reaction may develop years after treatment, and it is sometimes misdiagnosed as another skin condition not related to radiotherapy. Ionizing radiation can cause latent reaction on cellular level, which is clinically manifested as chronic radiation dermatitis. It includes changes in vascularity, pigmentation, fibrous tissue, number of cells, and others.

## Skin appearance, wounds, and ulceration

Chronic radiation dermatitis may be clinically visible as a change of skin appearance. It includes skin hypo- and hyperpigmentation, skin atrophy, hyperkeratosis, loss of skin appendages, hair follicles, sebaceous, and sudoriferous glands.<sup>2</sup> The common cosmetic defect after irradiation is telangiectasia – the dilation of small blood vessels.<sup>34</sup> Damage caused by ionizing radiation to the blood vessels may lead to insufficient oxygenation of the skin cells and predispose to ulceration and/or chronic wounds.<sup>2</sup> Moreover, this effect may be strengthened by skin atrophy and hyperkeratosis.<sup>35,36</sup> Weakened and dehydrated skin is sensitive to injuries, and the addition of hypoxia can cause severe and nonhealing wound or even skin necrosis.<sup>2</sup>

## RIF

RIF is commonly described as severe, progressive, and irreversible late complication of radiotherapy, but some literature data suggest that fibrotic changes may be reversible.<sup>37</sup> RIF may lead to cosmetic and functional defects, which can deteriorate patients' quality of life. It manifests in many ways,

which includes induration and retraction of the skin, lymphedema, joint motion restriction, changes in skin appearance, wounds, and ulcerations.<sup>38</sup> The fibrotic lesions are usually restricted only to the irradiated area. Adding a boost dose to particular area increases a risk of RIF.<sup>39</sup>

## Secondary cancers

Ionizing radiation may lead to the development of many form of skin cancers, especially basal cell carcinoma and squamous cell carcinoma.<sup>40,41</sup> Some studies suggest a connection between irradiation and melanoma.<sup>42</sup> Radiotherapy also increases a risk of chronic radiation keratosis and precancerous keratotic skin lesion.<sup>43</sup>

## Diagnosis and assessment

### Diagnosis

Diagnosis is usually made by taking a medical history and clinical examination. It should include a detailed information about radiotherapy (irradiated fields, irradiated volume, technique, dose, and fractionation), chemotherapy, surgery or other oncological interventions, previous skin complications after radiotherapy, comorbidities (connective tissue disorders and genetic disorders), and taken medications. Examination of skin is based on palpation and inspection. During the first examination, it is important to describe precisely the affected area (size, depth, morphological aspects, and color) to assess the efficacy of treatment in the future. In some cases, especially when the clinical presentation is unclear or suspicious, a biopsy and histopathological examination are obligatory. It includes conditions that may mimic chronic radiation dermatitis, such as secondary cancers, angiosarcoma, or radiation-induced morphea.<sup>44</sup> However, the biopsy or any other surgical intervention may deteriorate the course of RIF and cause prolonged wound healing.<sup>31</sup>

In some cases, the differential diagnosis between RIF and malignancy can be confirmed by magnetic resonance imaging (MRI).<sup>45,46</sup> Differential diagnosis should include nephrogenic systemic fibrosis (NSF, also known as nephrogenic fibrosis dermopathy). It is a serious condition with unknown cause that involves extensive fibrosis of skin, joints, and internal organs. It is suggested that pathophysiology of NSF may be associated with gadolinium-based MRI contrast agents.<sup>47</sup>

### Grading

In a routine clinical practice, two scales are used to assess the grade of chronic radiation dermatitis. They are summarized in Table 1. The toxicity criteria of the Radiation Therapy Oncology Group and the European Organization for Research and

Table 1 Assessment of chronic radiation dermatitis

Late adverse event	Scale	Grade	1	2	3	4	5
Skin reaction	RTOG		Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration	NA
Subcutaneous tissue reaction	RTOG		Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture >10% linear measurement	Necrosis	NA
Skin atrophy	CTCAE		Covering <10% BSA; associated with telangiectasias or changes in skin color	Covering 10%–30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration	–	–
Hyperpigmentation	CTCAE		Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	–	–	–
Hypopigmentation	CTCAE		Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	–	–	–
Skin induration	CTCAE		Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide, or pinch skin; limiting joint movement or orifice (eg, mouth, anus); limiting self-care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Skin ulceration	CTCAE		Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1–2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	Death
Telangiectasia	CTCAE		Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	–	–	–
Other skin and subcutaneous tissue disorders	CTCAE		Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

**Abbreviations:** ADL, activities of daily living; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Event; NA, not applicable; RTOG, Radiation Therapy Oncology Group.

Treatment of Cancer assess two aspects of chronic radiation dermatitis – skin and subcutaneous tissue.<sup>48</sup> More detailed assessment can be done through The Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

It includes skin atrophy, skin hyper- and hypopigmentation, skin induration, skin ulceration, telangiectasia, and other skin and subcutaneous tissue disorders.

It is known that acute radiation dermatitis in patients who receive radiotherapy combined with biological agents (such as cetuximab) has a different pathophysiological ground and clinical manifestation in comparison to radiation dermatitis caused by radiation therapy alone or given concomitantly with conventional chemotherapy. It was suggested that existing grading tools need a strong revision and a new grading system was proposed.<sup>49,50</sup> Currently, an international group of experts proposed a new classification that considers the CTCAE recommendations regarding the activities of daily living to assess acute bioradiation dermatitis.<sup>51</sup> However, there is no such grading system designed to assess chronic radiation dermatitis caused by combined radiation and biological agents therapy – this topic needs a separate expert consensus.

## Prevention

From the clinical perspective, the reduction in the incidence of chronic radiation dermatitis is expected especially for soft tissue sarcomas and breast or head and neck cancer patients due to the high dose received by skin and predictable long survival. The most important prevention method of chronic radiation dermatitis is the use of proper radiation therapy techniques to avoid unnecessary irradiation of healthy skin. It was shown that the application of intensity-modulated radiation therapy (IMRT) leads to the reduction of late radiation complications, for example, breast induration and telangiectasia.<sup>52,53</sup> IMRT allowed to reduce acute wound healing complication rates in patients with lower extremity sarcomas.<sup>54</sup> However, the results may vary depending on treatment site and localization of target volumes, thus preparing a few treatment plans in different techniques and comparing them is recommended. Another approach for skin sparing may be the avoidance of putting bolus when there is no necessity to ensure the full dose to targets near or at the skin. The trends in modern radiotherapy allow to use altered fractionation schedules, such as hypofractionation. It was shown that late skin reactions are related to the dose per fraction. Larger daily doses received by skin may increase the risk of chronic radiation dermatitis, so it is important to apply skin-sparing techniques of irradiation, but only when it is possible to obtain satisfactory dose coverage of target

volumes.<sup>55</sup> Further observations regarding late skin toxicity after new radiotherapy methods (particle therapy, stereotactic radiotherapy, and radiosurgery) are obligatory. To avoid severe skin toxicity, it is recommended to hold BRAF and MEK inhibitors 3 or more days before and after fractionated radiotherapy and 1 day or more before and after stereotactic radiosurgery (SRS).<sup>16</sup>

Literature data suggest that supplementation with antioxidants (eg, vitamin E, vitamin C, selenium, and melatonin) during radiotherapy may decrease radiation injury in healthy cells and enhance the immune response.<sup>56–58</sup>

## Treatment

Available literature data on the management of chronic radiation dermatitis are unsatisfactory. Most of the interventions are based only on clinical practice and extrapolation of management used in similar conditions.

## Telangiectasia

Telangiectasia is a form of chronic radiation dermatitis that may be psychologically distressing for a patient and cause physical disfiguration. The only method with limited evidence of efficacy is pulse dye laser therapy. In the retrospective study conducted at the Dermatology Division of Memorial Sloan-Kettering Cancer Center, 11 patients with telangiectasias received pulse dye laser therapy. The improvement was observed in all patients, including both physical appearance of the skin and general well-being.<sup>59</sup> In another study, the efficacy of the pulse dye laser in the treatment of postirradiation telangiectasia of breast or chest wall was investigated.<sup>60</sup> Eight patients were treated with this method, obtaining satisfactory clinical effect.

## Ulceration and necrosis

Chronic ulceration and necrosis are significant manifestations of chronic radiation dermatitis. Due to the effects caused by ionizing radiation, vascularization of ulcerated areas of skin is commonly very poor and refractory to conservative treatment. Some chronic postirradiation wounds may be treated with special dressings. Infected wounds may be covered by dressings, which contains silver, whereas wound with moderate or large exudation requires absorbent dressings.<sup>2</sup> Severe ulcerations and/or necrosis require surgical management, which includes methods from simple removal to advanced reconstructions with skin flaps or artificial skin.<sup>61,62</sup> The considerable, but not established in postirradiation ulcers, method of treatment is maggot debridement therapy. It involves the application of living disinfected fly larvae into the nonhealing skin and soft tissue wound. The aim is to clean

the wound from necrotic tissue and help it to heal.<sup>63</sup> In one case report, it was shown that low-intensity laser therapy for postirradiation chronic ulcer increases the number of dermal vessels, so this approach may be beneficial for patients with radiation ulcers and radiation necrosis.<sup>64</sup> A case study described by Wollina et al presents another method of treatment of chronic radiation ulcers with recombinant PDGF and a hydrophilic copolymer membrane.<sup>65</sup> *Hypericum perforatum* and neem oil may also be a considerable option in patients with severe chronic skin reaction; however, this combination of agents was tested only in the management of acute skin toxicity.<sup>66</sup> Refractory or nonhealing ulcers are always to be treated as being suspected of secondary malignancy.

## Fibrosis

The management of RIF is demanding. Available methods include rehabilitative care, pharmacotherapy, hyperbaric oxygen therapy, and laser therapy. Patients presenting RIF also require a supportive therapy (pain management, psychological support, wound care, and cosmetic interventions) to avoid the deterioration of quality of life.

### Rehabilitative care

Early initiation of rehabilitative care is beneficial for patients who are thought to be at high risk of RIF or who are at the early stage of its development. Although, even in patients with advanced RIF, rehabilitation should be considered as a therapeutic option. Bourgeois et al conducted a randomized, prospective clinical trial regarding the LPG technique in treating RIF in a group of 20 breast cancer patients divided into two groups (LPG technique vs observation only).<sup>67</sup> The LPG technique is described as a mechanical massage that allows skin mobilization by folding/unfolding. LPG treatment lead to decrease in erythema (10% vs 40% before treatment), pain and pruritus (10% vs 20% and 40% before treatment), and a feeling of induration of the skin (10% vs 70% before treatment). There is also a single case study describing the deep friction massage technique, which can reduce the symptoms of RIF, but this method needs to be proven in a larger group of patients.<sup>68</sup> Active and passive physical therapy may be useful in reducing contractors and improving movability.

### Pharmacotherapy

There is a lack of strong evidences for the use of pharmacological methods in the management of RIF, although several substances are used to treat this condition.

A few publications describe the beneficial effect of pentoxifylline, a methylated xanthine derivative. It works as a competitive nonselective phosphodiesterase inhibitor, which

increases concentration of intracellular cyclic adenosine monophosphate, activates protein kinase A, inhibits TNF and leukotriene synthesis, decreases granulocyte–macrophage colony-stimulating factor and interferon gamma, and suppress the TGF expression.<sup>38,69–73</sup> The suppression of TGF-beta may influence fibroblasts and reduce or even reverse fibrosis. It is sometimes used in combination with tocopherol (vitamin E). Results of small randomized clinical trials provided mixed data on the efficacy of aforementioned drugs combination.<sup>38,74–76</sup> In some of them, the effect of pentoxifylline ± tocopherol on RIF was not higher than placebo.<sup>75,76</sup> However, a study conducted by Delanian et al show a clear reduction of superficial fibrosis in a group of 44 women who received pentoxifylline (800 mg/day) plus tocopherol (1000 units/day) for 6–48 months.<sup>77</sup> A total of 37 patients were receiving therapy for 24–48 months, 7 patients discontinued treatment after 6–12 months. It was found that pentoxifylline and tocopherol need a prolonged amount of time (average 24 months) to obtain clinically significant effect manifested as reduction of RIF (68% of mean estimated maximal regression in surface area of RIF). Larger randomized clinical trials are required to confirm the efficacy of these drug combinations and to set the optimal dose and duration of therapy.

Other pharmacological interventions that were tested on limited group of patients are superoxide dismutase. Liposomal-encapsulated superoxide dismutase is an antioxidant enzyme that catalyzes the dismutation of superoxide radical into hydrogen peroxide and oxygen. It also works as a suppressor of TGF-beta in myofibroblasts, thus it may be effective in conditions with fibroblasts hyperactivity.<sup>26</sup>

In 1994, Delanian et al performed a clinical trial on a group of 34 patients with RIF.<sup>78</sup> Participants received liposomal-encapsulated superoxide dismutase >3 weeks in twice weekly intramuscular injections of 5 mg for a total of 30 mg. Some clinical regression of fibrosis in all patients was found.

### Hyperbaric oxygen

Some clinical data suggest that hyperbaric oxygen may have a positive impact on the reduction of late radiation toxicity; however, its efficacy in reducing the incidence of RIF has not yet been proven. Clinical research confirmed the benefits of hyperbaric oxygen in the management of lymphedema caused by conservative breast therapy.<sup>79,80</sup>

### Laser therapy

Clinical experience and data from other conditions suggest that laser therapy can stop the excessive fibrosis and induce normal scar remodeling in patients with RIF. In the ongoing

clinical trial NCT01910818 (pilot study of the effect of laser on reversing chronic radiation injury), research team proposed the use of fractional laser treatment to treat fibrosis associated with hypertrophic scars and morphea.<sup>81</sup> The final data collection date for the primary outcome measure is planned by the end of August 2017. Combination of laser therapy with epidermal grafting was also shown as an effective treatment method. Vietnamese researchers used laser therapy with epidermal skin grafting in three children with chronic radiation dermatitis after radiotherapy for infantile hemangioma. The obtained clinical result was satisfactory – skin repigmentation, softening, and increased flexibility were observed.<sup>82</sup>

### Surgical intervention

In extremely rare clinical situations (severe deterioration of quality of life, very limited movability, and pain that cannot be managed by other methods), a surgical intervention may be considered, but it can also potentially exacerbate fibrosis, thus the assessment of benefits vs risks ratio is mandatory.<sup>31</sup> The exceptional situation is the suspicion of tumor recurrence or second cancer formation where surgical approach is preferable over conservative methods or observation. One publication describes a study performed on a small group of patients with severe RIF after breast conserving therapy for breast cancer.<sup>83</sup> In these patients, surgeons performed partial mastectomy and latissimus dorsi muscle reconstruction obtaining a satisfactory reduction of symptoms.

### Further challenges

The rapid development of radiotherapy in the last 20 years allowed to introduce innovative techniques, such as IMRT. It provides a better dose homogeneity and allows to avoid hot spots on skin. However, application of IMRT may increase the volumes of tissues, which receive small doses, so comparison of treatment plans prepared in different techniques is recommended. Increasingly popular modern radiotherapy techniques based on prescribing a large dose of radiation to a small volume in one or a few fractions, such as stereotactic body radiotherapy (SBRT) and SRS, may cause another clinical manifestation of chronic radiation dermatitis, thus it is highly recommended to follow SBRT/SRS guidelines during treatment planning. Also there are no data concerning late skin toxicity of the new particles (protons, heavy ions), which become more available and used in clinical practice. Nonetheless, this may be relevant only in case of superficially located target volumes that are close to the skin. Another promising technology is 3D

printing of customized boluses. Conventional boluses have often fixed size. That increases an area of covered skin and may lead to higher skin toxicity. In addition, a process of bolus application may be inaccurate. Three-dimensional calculated and printed bolus may allow to deliver a dose to target tissues with avoidance of healthy skin.<sup>84</sup> Moreover, a rapid development of targeted therapy and immunotherapy with concomitant radiotherapy opens a new field for potential side effects related to skin. Increasing knowledge about genomics and radiomics will allow scientists and clinicians to select patients who are at risk of the development of chronic radiation dermatitis, so a prophylaxis and special caution may be implemented before and after irradiation. Novel agents and treatment modalities, such as antioxidants or inflammation suppressors, are under investigation. These include superoxide dismutase and catalase mimetics, curcumin, and quercetin.<sup>85–87</sup>

### Conclusion

Chronic radiation dermatitis can develop years after radiotherapy. Its manifestations, such as RIF, may cause disfiguring cosmetics effect, reduce mobility, and severely impair patients' quality of life. It is dependent on the dose, irradiated volume, and other factors, such as comorbidities and individual predispositions. The choice of proper radiotherapy technique, dose, and fractionation may reduce a risk of radiation-induced dermatitis. However, it should not be prioritized over the main aim of irradiation – proper dose coverage of target volumes and achieving the highest probability of tumor control. There are several treatment modalities that can be approached to reduce symptoms of chronic radiation dermatitis, but they are not based on strong scientific evidence, thus their value is limited. A novel treatment methods and clinical trials are strongly needed to provide more efficacious therapies for this radiotherapy complication.

### Disclosure

The author reports no conflicts of interest in this work.

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