

Original article

Acute Skin Toxicity in Breast Cancer Patients Following Different Fractionation Regimens of Postoperative Radiotherapy

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SUMMARY

Introduction/Aim. Breast cancer (BC) represents a globally significant health issue, with incidence rates varying worldwide. Radiotherapy is crucial in treating BC, however, it can cause adverse effects, including skin reactions. The aim of this research was to evaluate the impact of two different radiotherapy fractionation regimens on the occurrence and severity of acute skin toxicity in BC patients.

Methods. The prospective study involved 44 patients who underwent postoperative radiotherapy. The patients were randomly divided into two groups: one group received hypofractionated regimen (40.05 Gy in 15 fractions over three weeks), while the other group received the standard fractionated regimen (50 Gy in 25 fractions over five weeks). The patients in this study were monitored weekly for acute skin toxicity throughout the duration of radiotherapy and following the completion of treatment.

Results. The patients receiving the standard fractionated regimen experienced a higher frequency and intensity of acute skin reactions, including erythema, dry desquamation, and moist desquamation. Skin reactions of grade I and II were particularly prominent in the patients receiving 50 Gy. Although the patients receiving hypofractionated radiotherapy had less severe skin reactions, mild skin changes did occur, although they were generally less prominent.

Conclusion. The study points to the need for a careful selection of fractionation regimens in postoperative breast radiotherapy. Additionally, this study contributes to the understanding of the relationship between different radiotherapy modalities and the occurrence of acute skin toxicity, providing guidelines for optimizing treatment in BC patients.

Keywords: breast cancer, breast-conserving surgery, radiotherapy, radiodermatitis

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INTRODUCTION

Malignant breast tumors (BC) represent a global health problem today since they are the most frequently diagnosed malignant disease in women worldwide (1). According to the World Health Organization, it is estimated that there were over 2.3 million new cases of BC in 2020, accounting for 11.7% of all new cases, with significant impacts on the healthcare system and individuals (2). The incidence varies from country to country, with higher prevalence in developed countries compared to developing ones, which is attributed to differences in lifestyle, hygienic-dietary habits, access to preventive measures, and genetic predisposition (3). The high morbidity and mortality rates (3, 4) associated with BC were the stepping stones to efforts to enhance therapeutic approaches with a view to reducing incidence and improving treatment outcomes.

A multidisciplinary therapeutic approach involves the application of surgery, chemotherapy, hormone therapy, targeted therapy, and radiotherapy to achieve the best possible outcome for patients. Radiotherapy is an essential component in the modern therapeutic approach, aimed at controlling the disease from its earliest stage to metastatic phases (5, 6). Despite its justified and almost constant use, it can be accompanied by a range of acute adverse effects including fatigue, skin reactions, pain, stress, and reduced quality of life.

During radiotherapy, healthy tissue, including skin, is inevitably exposed to radiation doses that can lead to varying degrees of damage (7). Acute skin toxicity encompasses a broad spectrum of manifestations, from mild erythema and skin dryness to more severe forms such as moist desquamation, ulceration, and necrosis (1, 8). These skin reactions can significantly affect the quality of life of patients, causing pain, discomfort, and even social isolation due to aesthetic consequences. Moreover, severe skin reactions may require treatment interruption or delay, which can compromise treatment efficacy.

The fractionation regimen of radiotherapy is one of the most important factors influencing the occurrence and severity of acute skin toxicity (9, 10). Standard regimens involve the application of lower radiation doses over a longer period of time, such as the widely used regimen of 25 fractions over five weeks, with a daily dose of 2Gy, which may result in fewer skin reaction (11). In contrast, hypofractionated regimens, which involve higher doses of radia-

tion over a shorter period, offer certain advantages such as shorter treatment duration and greater convenience for patients but may lead to more prominent skin reactions during treatment (12). Research on different fractionation regimens and their association with acute skin toxicity is crucial for treatment optimization, with studies giving contradictory conclusions, making it difficult to establish general recommendations.

AIMS

This study aims to assess the impact of two commonly recommended fractionation regimens of postoperative radiotherapy on the occurrence and degree of acute skin toxicity in BC patients, comparing conventional fractionation (CF) with hypofractionated radiotherapy (HF).

PATIENTS AND METHODS

Patient selection

Patients involved in this prospective study underwent their active treatment by means of postoperative radiotherapy between October 2023 and March 2024, at the Radiotherapy Daily Hospital of the Oncology Clinic at the University Clinical Center Niš. They were informed about the study during their initial consultation. Detailed explanations regarding the study's purpose and methods were provided, and written consent was obtained from all participants. This study received an approval from the Ethics Committee of the University Clinical Center Niš, under the number 30414/5. Written informed consent was obtained from all patients included in the study.

The selection included women over 40 years of age with pathologically confirmed ductal carcinoma *in situ* (DCIS) or invasive breast cancer, stage Tis-T2, N0-N1a, M0. General data about patients, tumor characteristics, and previous treatments (tumor type, grade, resection margin status, hormonal status, previous neoadjuvant or adjuvant chemotherapy, concomitant use of targeted or hormonal therapy) were obtained from medical records. Patients were matched by gender, age, and disease stage. All patients had previously undergone breast-conserving surgery. The surgical procedure included palpation-guided lumpectomy for palpable tumors, while for non-palpable tumors wire-guided or ultra-

sound-guided lumpectomy was used, with negative resection margins on the definitive histopathological specimen. Axillary region surgery included sentinel lymph node biopsy (SN) or axillary lymph node dissection (ALND). Adjuvant chemotherapy, targeted, or hormonal therapy was administered according to the histological characteristics of each patient's tumor and in accordance with national guidelines (13).

The radiotherapy treatment plan included whole breast irradiation (WBI) without adding additional fields to cover regional lymph nodes and tumor bed, so as to make the study groups homogeneous.

Exclusion criteria included the presence of synchronous malignancies, a history of previous breast cancer treated with radiotherapy, bilateral breast cancer, previous radiotherapy in the current radiation area, use of statins in personal therapy, radically operated breast tumors, axillary node status greater than N1a, male gender and unwillingness of the patient to undergo regular follow-ups and check-ups at the radiotherapy ambulance.

Patients were randomly selected to receive either hypofractionated whole breast irradiation (HF-WBI) with a therapeutic dose of 40.05 Gy in 15 fractions over three weeks or standard fractionated whole breast irradiation (CF-WBI) with a therapeutic dose of 50 Gy in 25 fractions over five weeks.

Preparation and method of radiotherapy administration

Preparation for radiation treatment included simulation using a General Electric CT scanner, with patients positioned in a supine position with their arms raised above their head, utilizing appropriate immobilization equipment, specifically an extended wing board in this case. The clinical target volume (CTV) of the breast to be treated was defined using radiopaque markers, as a precondition for easier delineation of target volumes. Delineation of target volumes and organs at risk (OAR) was performed according to national and international guidelines (13-15). The target volume of interest referred to the remaining post-surgery breast tissue, with delineation of the contours of OAR in close anatomical proximity. A protocol margin of 0.7 mm was added to cover inter/intra-fractional errors.

Patients were scheduled to undergo three-dimensional conformal radiotherapy (3DCRT) using

megavoltage tangential fields, with beforehand directed planning technique, with the potential addition of segmental fields in order to enhance dose homogeneity. The dose ranged from 95% to 105% of the prescribed dose within the clinical target volume, and the dose to structures outside the treated breast was limited according to the care standard. After the planning phase, therapeutic plans were reviewed, which included the evaluation of dose distribution, color wash dose representation, and dose-volume histograms in order to ensure the appropriateness of the radiotherapy plan. Radiotherapy treatment commenced between 21 and 63 days after the last surgical intervention or the final cycle of adjuvant chemotherapy.

Assessment of skin toxicity

The patients in this study were monitored weekly for acute skin toxicity throughout the duration of radiotherapy. Following the completion of treatment, they were monitored weekly for up to eight weeks since the beginning of the treatment. The next check-up was scheduled three months after the treatment. Additional toxicity assessments were conducted at the discretion of the physician and/or based on the patient's needs. Acute skin toxicity is defined as skin reaction in the irradiated area of the breast occurring during the radiotherapy course or within two months after its completion. The data were noted down as part of personal medical history, and the assessment of skin damage and classification of these acute skin reactions as a result of radiotherapy administration were conducted using the Radiation Therapy Oncology Group (RTOG) scale (16), which includes criteria for the assessment of morbidity caused by radiation. In order to classify the effects of radiotherapy, these criteria categorize the severity of skin reactions into five grades: grade 0 (no reaction), grade 1 (mild erythema, dry desquamation, epilation, or reduced sweating), grade 2 (moderate, rapid erythema, exudative dermatitis in the form of plaques, and moderate edema), grade 3 (exudative dermatitis with involvement of skin folds, and intense edema), and grade 4 (ulceration, bleeding, or necrosis).

Statistical analysis

Data are presented as frequency distributions expressed as percentages or mean values with stan-

dard deviations. Normality distribution was confirmed by Kolmogorov–Smirnov test. The comparison of mean values was done using the Student's t-test, while in case of categorical variables, the Chi-squared or Fischer's exact test was used. Values of $p < 0.05$ were considered to be statistically significant. The statistical package SPSS (version 21.0, IBM Corp, 2012; NY, USA) was used for data processing.

RESULTS

The research involved monitoring and assessing acute skin toxicity in 44 patients with BC. These patients were divided into two groups of 22 patients each: the Gy40 group, which received 40.05 Gy dose in 15 fractions over three weeks, and the Gy50 group, which received 50 Gy dose in 25 fractions over five weeks. The research results, including the socio-demographic characteristics of the patients with BC who participated, are given in Table 1.

Table 1. Sociodemographic characteristics of the breast carcinoma

	Group I – Gy40 (n=22)	Group I – Gy50 (n=22)	p value
Age (mean ± SD)	61.9 ± 8.5	50.2 ± 10.4	> 0.05
Type of carcinoma			
Ductal	17	16	> 0.05
Lobular	1	5	
Ductal-lobular	4	1	
Disease stage			
T1 N0	11	16	> 0.05
T2 N0	11	6	
Type of chemotherapy			
Neoadjuvant	4	2	> 0.05
Adjunctive	7	3	> 0.05
Target	4	0	0.036
Hormonal	20	21	> 0.05

The average age of patients in the Gy40 group was 61.9 years, while in the Gy50 group it was 50.2 years. Statistical analysis did not reveal a significant difference in age between the groups ($p > 0.05$).

Regarding the histopathological confirmation of BC, 17 patients in the Gy40 group and 16 patients in the Gy50 group had patohistologically verified ductal BC. Lobular BC was detected in one patient in the Gy40 group and in five patients in the Gy50 group. Ductal-lobular carcinoma was diagnosed in four patients in the Gy40 group and in one patient in the Gy50 group. Analyzing the histopathological types of carcinoma in the studied groups, no statistically significant difference was found (Table 1). In addition, there was no statistically significant difference in disease stage ($p > 0.05$), with both

groups including patients with early-stage BC (Table 1).

The research results obtained by the analysis of the applied systemic treatments, including chemotherapy, targeted therapy, and hormonal therapy in neoadjuvant and adjuvant approaches, did not show a statistically significant difference between the groups, except in the subgroup receiving targeted therapy ($p = 0.036$). Targeted therapy in the neoadjuvant approach, and subsequently adjuvant up to one year according to care standard, was administered to four patients in the Gy40 group, whereas there were no patients in the Gy50 group who underwent this therapeutic approach.

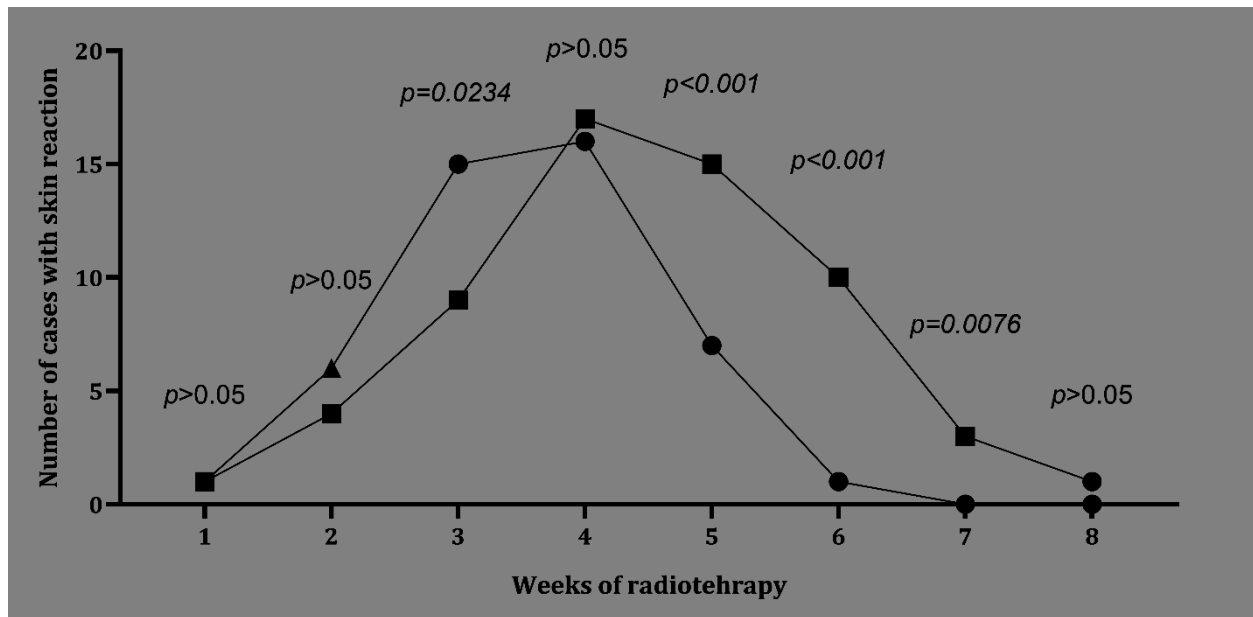


Figure 1. Frequency of cases with skin reaction to different radiotherapeutic modalities during an eight-week period – Gy40 (square) and Gy50 (circle)

The frequency of skin reactions over the 8-week period is shown in Figure 1. Throughout this period, patients were monitored for dose differences between modalities, with a slightly higher frequency observed in the group receiving the standard dose regimen of 50 Gy in 25 fractions compared to the hypofractionated regimen of 40.05 Gy in 15 fractions. Statistically significant increases in skin lesions were noted in the 3rd, 5th, 6th and 7th week in the patients receiving the standard dose regimen of TD 50 Gy.

In addition to assessing the incidence of acute skin reactions, the research also evaluated the severity of superficial skin damage, in particular the occurrence of radiodermatitis of grade I (erythema), grade II (dry desquamation), and grade III (moist desquamation) among patients receiving different radiotherapy modalities in the Gy40 and Gy50 groups (Table 2).

Type I was the most common and was observed more frequently in the patients treated with 50 Gy compared to those treated with the hypofractionated regimen of 40.05 Gy (Figure 2). This frequency was statistically significantly higher in weeks 5 and 6 of therapy.

Table 2. Statistical comparison between the total skin reaction occurrence in patients treated with different radiotherapeutic modalities

	Group I – Gy40	Group I – Gy50	p value, Chi-square
Type I	46	60	0.043, 6.292
Type II	2	13	
Type III	0	2	

Type II was significantly more prevalent in the Gy50 group compared to the Gy40 group, with significant differences in the frequency of occurrence of these reactions in weeks 5 and 6.

Type III was recorded only in two patients who received 50 Gy. However, a small sample size limits the possibility to achieve statistical significance compared to the Gy40 group, where no patients exhibited this type of reaction (Figure 2).

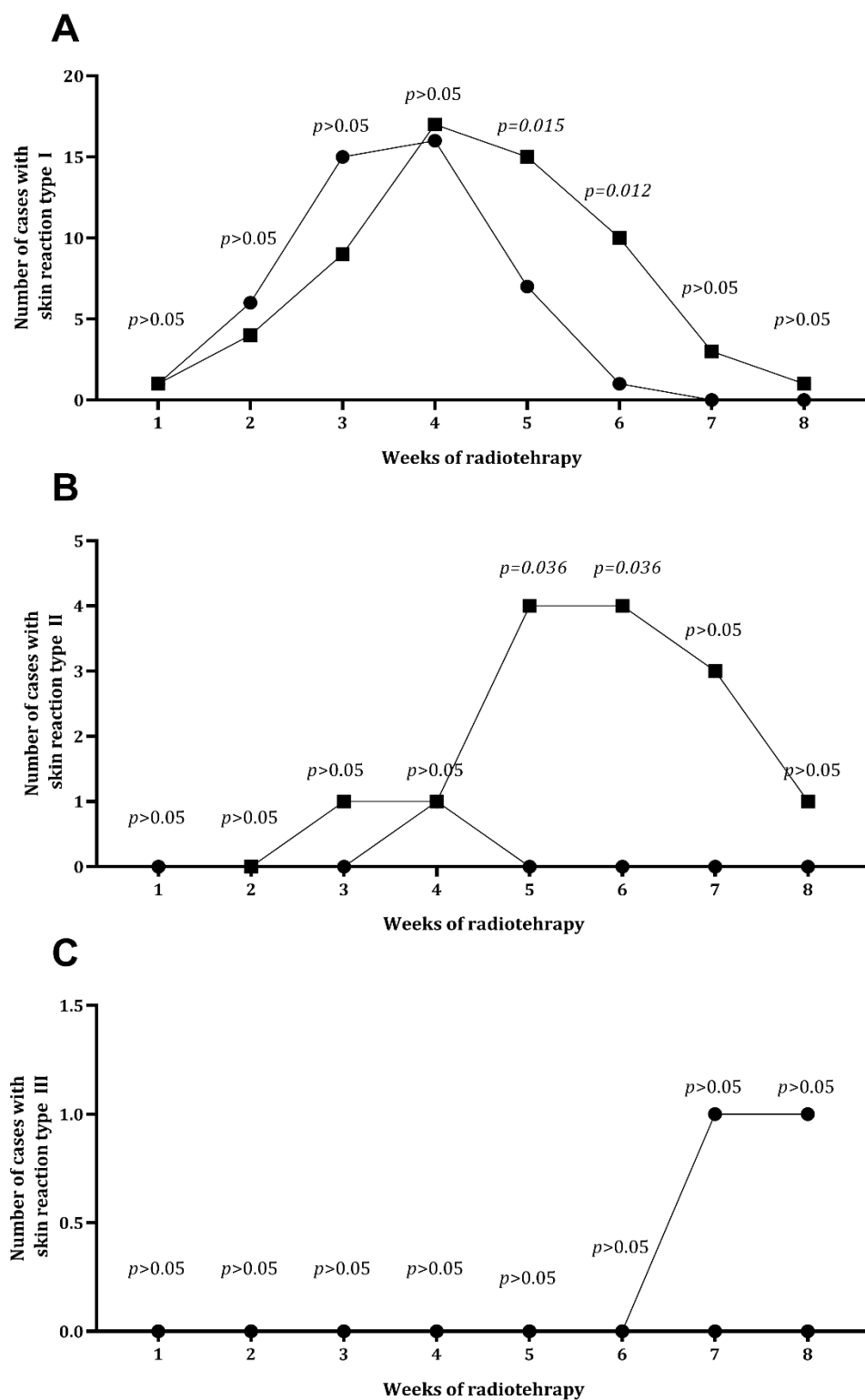


Figure 2. Frequency of cases with different degree (I – A; II – B; III – C) of skin reaction in relation to different radiotherapeutic modalities during an eight-week period – Gy40 (circle) and Gy50 (square)

DISCUSSION

Breast-conserving surgery (BCS) combined with postoperative radiotherapy has become the standard approach for treating early-stage BC. However, in order to be applied, it must be medically justified based on the disease stage, histopathological characteristics of the malignant cells, and patient preferences (17, 18). The rationale behind this treatment stems from numerous studies showing improved outcomes in clinical practice in terms of local control, distant disease relapse control, and overall survival (19-21). Without compromising oncological outcomes, this mode of treatment results in better cosmetic outcomes, which is crucial for the patient's quality of life (22-24). The introduction of ionizing photon radiation into clinical practice, generated in radiotherapeutic devices like linear electron accelerators, has enabled the broad application of radiotherapy following lumpectomy. This has enabled the elimination of residual cancer cells in the breast, significantly reducing the risk of locoregional recurrences and contributing to the extension of survival for breast cancer patients (25, 26). This treatment is particularly important for patients with invasive BC, when lymph nodes are also affected or following mastectomy, especially for those with high risk of disease recurrence (27, 28).

The results of this study indicate that the patients were approximately of the same age, with the exception of those in the Gy50 group, who were slightly younger on average, which is in accordance with the care standard in our country. It is also important to note that individual patient factors such as skin type, age, comorbidities, and genetics can significantly impact the occurrence of acute skin toxicity. Some patients may be naturally more resistant to radiation, while others may be more prone to toxicity regardless of the fractionation regimen. It has been highlighted in multiple studies that radiation chemically damages the skin, and the use of statins has been identified as a potential initiator of radiodermatitis (29). The patients involved in this study did not receive this therapy in order to make a better assessment.

No statistically significant differences in cancer type or disease stage between the groups were found, suggesting that patients in both groups had similar basic tumor characteristics. This is important for the study's homogeneity as it allows valid comparisons of the effects of different radiotherapy

doses. On the other hand, it is important to emphasize that a significant difference in the use of targeted therapy between the groups was noted. This finding may impact study outcomes, as targeted therapy might have a synergistic effect with radiotherapy (30), which could be considered a study limitation.

The frequency of skin reactions was higher in the Gy50 group, which is expected given the higher radiation dose. However, the observed difference was not drastic, which may indicate good tolerance of higher doses of radiotherapy or the effectiveness of protective measures applied during the treatment, such as the use of moisturizers and skin care products. A study by Lee et al. reported a similar incidence, with 97.3% of cases of radiodermatitis among 111 women with BC in South Korea, although the radiotherapy technique used was not specified (31). Having taken this into consideration, it should be noted that in order to make the group homogenous, all patients in this study underwent three-dimensional conformal radiotherapy (3DCRT) on the treated breast volume, using the opposing tangential fields and additional segmental fields if necessary, for better dose distribution. Patients whose treatment plans required additional fields for the treatment of lymphatics and boost doses on the tumor bed were excluded from the study.

Initial research conducted after the introduction of hypofractionated postoperative breast radiotherapy brought about some uncertainty regarding this protocol's benefits (32), as it could be associated with significant acute and late toxic effects, such as soft tissue necrosis and fibrosis. These concerns and conclusions were likely due to limited knowledge in the field of radiobiology, resulting in the application of lower doses per fraction. Consequently, there was apprehension regarding acute complications with new dose regimens including the application of higher daily doses than the standard ones, as ionizing radiation inevitably affects the skin even when targeted at the tumor-affected tissue. On the other hand, more significant skin toxicity was observed in a study conducted in Brazil, where 100% of 86 women developed skin reactions after radiotherapy with a linear accelerator, receiving a total dose of 50.4 Gy (daily dose of 180 cGy) (33), which to some extent aligns with the results of this study.

Analyzing clinical data, Qi XS et al. obtained encouraging results indicating that the α/β ratio in BC cells is low, providing a basis for introducing

hypofractionated regimens into clinical practice (34). Such an approach proved to be useful during crisis situations like the COVID-19 pandemic, given the increasing number of patients, limited medical personnel, and restricted technical capabilities of the health centers. Studies like the Standardization of Breast Radiotherapy (START-B) and the Ontario Cooperative Oncology Group (OCOG) also highlighted equivalent tumor control with better cosmetic outcomes and late toxicity when using hypofractionated regimens of 40 to 42.5 Gy with daily doses greater than 2 Gy compared to traditional regimens (26, 35). Consequently, hypofractionated radiotherapy for BC has become part of the care standard in our institution, alongside standard protocols involving the application of a therapeutic dose of 50 Gy over five weeks.

This research also assessed the severity of damage during routine check-ups conducted from the first to the eighth week, employing the RTOG scale for skin toxicity. The results show a statistically significant difference in the occurrence of grade I radio dermatitis, specifically the occurrence of erythema in the group treated with standard fractionation of 50 Gy. This is a familiar outcome, as erythema is one of the most common acute skin manifestations of the applied treatment (36). Given that the tissue has a high proliferative index, which makes it highly radiosensitive, this outcome is justifiably one of the most frequent complications of radiotherapy (37). Encouraging results have been obtained by means of comparative analysis which indicates that patients in the hypofractionated group treated with 40 Gy experienced fewer acute adverse effects, manifested as skin reactions, which is in accord with recent clinical research (38). A large multicenter study found that hypofractionation regimen improved patient comfort and reduced dermatitis incidence in patients undergoing postoperative radiotherapy for BC. Consistent with these studies, the obtained results also suggest that the hypofractionated regimen could lower the risk of radiation dermatitis compared to the standard fractionation applied until now (39).

The absence of significant differences between HF and CF regimens suggests that the choice of fractionation regimen should be based on other factors, such as patient comfort, treatment duration, logistical requirements, and patient preferences. Hypofractionated regimens, due to their shorter treatment duration, may be preferable for patients who favor a shorter treatment period or face logistical challenges with longer treatment. Considering these research results along with reduced treatment costs and increased patient convenience (40-42), hypofractionation is justifiably part of the leading radiotherapy guidelines and protocols as a superior and cost-effective treatment option.

CONCLUSION

Despite significant advancements in medicine and technology, the number of breast cancer patients continues to rise, necessitating further research and development of effective strategies for prevention, early detection, and treatment, as well as improving the quality of life for patients after treatment. The current challenge is to minimize morbidity caused by radiotherapy while preserving efficacy at the same time. This study contributes to a better understanding of the incidence of acute adverse effects of postoperative radiotherapy for breast cancer and aids in shaping clinical practice recommendations with a focus on reducing acute toxicity and improving tolerance of hypofractionated radiotherapy treatments. The results suggest that, despite differences in radiotherapy dose, there are no significant differences in the basic characteristics of patients, and that higher doses of radiotherapy are associated with slightly higher incidence of skin reactions. It is important to emphasize that a careful selection of daily dose and total dose of radiotherapy can significantly impact the balance between treatment efficacy and minimizing side effects. Thorough consideration of this balance will aid in better understanding regarding treatment planning for individual patients.

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Akutna kožna toksičnost kod pacijentkinja sa karcinomom dojke nakon različitih režima frakcionisanja postoperativne radioterapije

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SAŽETAK

Uvod/Cilj. Karcinom dojke predstavlja značajan zdravstveni problem na globalnom nivou, sa incidencijom koja varira širom sveta. Savremeni terapijski protokoli uključuju multidisciplinarni pristup koji kombinuje hirurgiju, hemoterapiju, hormonoterapiju, ciljanu terapiju i radioterapiju. Radioterapija je ključna u tretmanu karcinoma dojke, ali može izazvati neželjene efekte, među kojima su i reakcije na koži. Cilj ovog istraživanja bio je da se proceni uticaj dvaju različitih režima frakcionisanja radioterapije na pojavu i težinu akutne kožne toksičnosti kod pacijentkinja sa karcinomom dojke.

Pacijenti i metode. Prospektivna studija je obuhvatila 44 pacijentkinje koje su podvrgnute postoperativnoj radioterapiji. Pacijentkinje su bile nasumično raspoređene u dve grupe: jedna grupa je tretirana hipofrakcionisanim režimom (40,05 Gy u 15 frakcija tokom tri nedelje), dok je druga grupa primala standardni frakcionisani režim (50 Gy u 25 frakcija tokom pet nedelja). Kod pacijentkinja je u toku tretmana na nedeljnom nivou vršena procena akutne kožne toksičnosti.

Rezultati. Rezultati istraživanja su pokazali da su kod pacijentkinja koje su primale standardni frakcionisani režim učestalost i intenzitet akutnih kožnih reakcija, uključujući eritem, suhu deskvamaciju i vlažnu deskvamaciju, bile veće. Reakcije kože gradusa I i II bile su naročito izražene kod pacijentkinja iz grupe koja je primala 50 Gy. Mada su pacijentkinje koje su primale hipofrakcionisanu radioterapiju imale manje ozbiljne kožne reakcije, pojavile su se blage promene na koži, koje su generalno bile slabije izražene.

Zaključak. Ova studija je ukazala na to da je potrebno pažljivo odabrati režim frakcionisanja u postoperativnoj radioterapiji dojke. Takođe, doprinela je razumevanju odnosa između različitih radioterapijskih modaliteta i pojave akutne kožne toksičnosti, pružajući pritom smernice za optimizaciju tretmana kod pacijentkinja sa karcinomom dojke.

Ključne reči: rak dojke, pošteditna operacija dojke, radioterapija, radiodermatitis