Factors on Development and Severity of Acute Radiodermatitis: Prospective Single-Centre Study

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Abstract

Background: Although prior literature has examined the treatment and patient-associated factors affecting the development and severity of acute radiodermatitis, there are relatively few prospective studies evaluating both.

Aims and Objectives: This study was prospectively designed to evaluate factors affecting the development and extent of radiation-induced acute skin toxicity called radiodermatitis (RD).

Materials and Methods: A total of 63 patients who underwent radiotherapy (RT) in Ankara Atatürk Research and Education Hospital between 20.06.2016 and 21.10.2017 were evaluated. Patients' demographic status, disease/treatment details, anemia, and diabetic profile tests' (hemoglobin, ferritin, folic acid, Vit B12, and hemoglobin A1c) were recorded. The development and the degree of RD were assessed weekly by treating radiation oncologists using Radiation Therapy Oncology Group (RTOG) radiation toxicity manual.

Results: The development of any grade of RD was not significantly affected by gender, concurrent chemotherapy (CT), pre-RT CT, the comorbid disease, RT technic, and anemia & diabetic profile tests' values. The development of grade 2-3 RD was significantly affected by the number of operations (p = 0.032) and total dose of RT (p = 0.008). The starting dose for RD is 20 Gy in patients with grade 2-3 RD and 32 Gy in patients with grade 1 RD (p = 0.018).

Conclusion: There was no significant relationship between RD and anemia/diabetic profile parameters. The severity of RD was associated with recurrent surgical intervention, total dose, and early onset of RD.

Introduction

Radiotherapy remains an essential component of cancer treatment, with nearly ½ of all cancer patients receiving RT during their illness (Lee et al. 2017). Radiodermatitis (RD) is skin toxicity of ionizing radiation, and approximately 95% of cancer patients receiving RT experience some form of RD, including erythema, dry and moist desquamation. These skin reactions often cause itching, pain, and sometimes treatment interruption and can lower the aesthetic appearance and quality of life in the long run. However, RD is mostly moderate, with only 15–25% of it is severe (Pires et al. 2008; Bonner et al 2006). RD is often observed in patients receiving breast, head and neck, vulva, and sarcoma RT (Pires et al. 2008; Bonner et al 2006; Sourati et al 2018). The underlying causes be examined under two main headings: Treatment and patient-related factors (Table 1).

Table 1
Factors affecting RD

Treatment-related parameters	Patient-related parameters
Total dose	Obesity
Field Size	Diabetes mellitus
Fraction dose	Malnutrition
Energy	Ethnic origin
Use of bolus	Age
Number of beams	Sex
Type of chemotherapy	Smoking
Overall treatment time	Genetic factors
	Stage

RD: Radiodermatitis

In previous studies, the relationship between these factors and RD has been investigated for different types of cancer (Sourati et al 2018; Porock et al. 1998). It is emphasized that some anemia parameters such as Ferritin, B12, Folic acid should be evaluated in relation to RD (Sourati et al 2018). In this prospective study, we aimed to evaluate the factors associated with the formation and extent of acute RD to find the high-risk group.

Materials And Methods

The study was conducted in accordance with the Helsinki Declaration, which the Ethics Committee approved of Ankara Atatürk Training and Research Hospital in February 2016. Between 20.06.2016-21.10.2017, 63 adult patients with stage 1–4, according to AJCC 8, treated with curative RT for head and neck, breast, vulva, sarcoma, and skin cancer in a tertiary radiation oncology clinic in Ankara were evaluated prospectively. Patient files and hospital electronic system data were used for data collection. The patients' demographic status, tumor size, disease stage, adjuvant treatment, weekly acute side effect assessment, and various treatments were noted. The anemia and diabetic profile tests' values (hemoglobin, ferritin, folic acid, B12, and hemoglobin A1c) of patients were assessed upon admission to RT clinic within a week before RT start. The primary endpoint is the evaluation of the formation and degree of acute RD. Skin changes in the RT field were examined by the same physician every week according to the Radiation Therapy Oncology Group (RTOG) manual in order to prevent inter-observer differences (Table 2) (Cox 1995). The degree of RD is divided into 2 groups: grade 0–1 RD and grade 2–3 RD. Patients who were not followed up for acute side effects regularly were excluded from the study.

Table 2
RTOG acute radiation morbidity scoring criteria in skin[6]

Grade	Change
0	No change over baseline
1	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating
2	Tender or bright erythema, patchy moist desquamation/moderate edema
3	Confluent, moist desquamation other than skin folds, pitting edema
4	Ulceration, hemorrhage, necrosis

RTOG: Radiation Therapy Oncology Group

Non-parametric tests were used because the variables were distributed normally with visual and analytic methods. Mann-Whitney U test was used for the independent 2 groups. In the categorical two variables analysis, Chi-Square and Fisher -s Exact tests were used. IBM SPSS Statistics 20.0 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) was used for statistical analysis and calculations. The level of statistical significance was accepted at $p < 0.05$.

Results

The patients' demographics are summarized in Table 3. The results of the anemia and diabetic profile values of the patients are presented in Table 4. RT technique ($p = 0.67$), gender ($p = 0.27$), concomitant CT ($p = 0.58$), preRT CT ($p = 0.57$), age ($p = 0.60$), the presence of DM ($p = 0.50$), and A&D profile were not significantly affecting the formation of RD.

Table 3
Patient demographics

Gender	Male	25(%38.1)
	Female	38(%60.3)
RT Technique	IMRT	39(%61.9)
	3DRT	24(%38.1)
Primer	Head and Neck	22(%34)
	Breast	28(%44)
	Skin	6(%9.5)
	Sarcoma	4(%6.3)
	Vulva	3(%4.8)
Stage	1	7 (%11)
	2	22(%34.9)
	3	25(%39.7)
	4	8(12.7%)
	DCIS	1(%1,6)
Operation	No	16(%25.4)
	Yes	47(%74,6)
Concurrent CT	Yes	35(%55,6)
	No	28(%44.4)
CT before RT	Yes	36(%57.1)
	No	27(%42.9)
Comorbide Disease	Yes	36(%57.1)
	No	27(%42.9)
DM	Yes	13(%20.6)
	No	50(%79.4)
Smoking	Smoker	50(%79.4)
	Non- smoker	27(%42.9)

IMRT: Intensity Modulated Radiation Therapy, *3DRT*: 3 Dimensional Radiotherapy, *DCIS*: Ductal Carcinoma In Situ, *CT*: Chemotherapy, *RT*: Radiotherapy, *DM*: Diabetes Mellitus, *RD*: Radiodermatitis

RD	Yes	60(%95.4)
	No	3(%4.8)
Grade of RD	0	3(%4.8)
	1	34(%54)
	2	25(%39.7)
	3	1(%1.6)

IMRT: Intensity Modulated Radiation Therapy, *3DRT*: 3 Dimensional Radiotherapy, *DCIS*: Ductal Carcinoma In Situ, *CT*: Chemotherapy, *RT*: Radiotherapy, *DM*: Diabetes Mellitus, *RD*: Radiodermatitis

Table 4
Anaemia and diabetic profile parameters

Parameters	Values (median)
Haemoglobin	12.4 (8.7–16.4)
Ferritin	104 (9.72–1269)
HbA1c(For DM +)	5.8 (5.46–9.05)
B12	322(159–1630)
Folic acid	7.2 (1.75-20)
Fasting Blood Glucose	83 (60–185)
Postprandial Blood Glucose	110 (105–276)

In the whole study population, 47 patients (74.6%) underwent surgery: 40 (85.1%) of them had 1, and 7 (14.9%) of them had 2 or more operations. Grade 2/3 RD was observed in 14 (35%) of the patients with 1 operation and 6 (85.7%) of the patients with more than 1 ($p = 0.032$). A significantly higher rate of grade 2/3 RD was observed in patients with 2 or more operations ($p = 0.032$).

No significant effect of RT fraction dose (1.8Gy vs. 2 Gy vs. 2.67 Gy) on RD was observed. A significant relationship was observed between RT total dose and grade 2/3 RD ($p = 0.008$) (Fig. 1). The median total dose was 50 Gy (range, 39–70) in patients with Grade 0/1 RD and 60 Gy in patients with grade 2/3 RD (range, 50–70) ($p = 0.008$). The probability of grade 2/3 RD increased significantly with increasing total doses.

In patients with grade 2/3 RD, the initial dose RD was 20 Gy (range, 14–36), and in patients with grade 1 RD, the initial RD dose is 32 Gy (range, 16–56) ($p = 0.018$) (Fig. 2). The lower the initial dose of RD, the higher the risk of grade 2/3 RD.

Discussion

In our study, no significant effect was found between RD development and blood levels of anemia and diabetic profile parameters. However, grade 2/3 RD is significantly affected by the number of operations performed by the patient before RT ($p = 0.032$). A significantly higher rate of grade 2/3 RD was observed in patients with an operation number of 2 or more. A significant relationship was also observed between RT total dose and grade 2/3 RD ($p = 0.008$) (Fig. 1). The median total dose was 50 Gy (range, 39–70) in patients with grade 0/1 RD; and 60 Gy (range, 50–70) in patients with grade 2/3 RD ($p = 0.008$). In addition, patients with grade 2/3 RD had a median initial dose of 20 Gy (range, 14–36); In patients with grade 1 RD, the initial generation dose of RD was 32 Gy (range, 16–56) ($p = 0.018$). The lower the threshold dose of RD, the higher the risk of grade 2/3 RD.

Radiation exposure to the skin causes cellular damage, aggravated by ROS formation and nucleic acid damage, and migration of inflammatory cells in the skin, and eventually, RD develops (Malkinson and Keane 1981). Cellular damage is mainly observed in epidermal cells, basal epidermal cells, Langerhans cells, endothelial and vascular cells (Brown and Rzucidlo 2011).

Increased cellular damage leads to an induced inflammatory cytokine and chemokine cascade. Chemokines and cytokines such as IL-1, IL-6, TNF-alpha, TGF-Beta, and histamine-like mediators increase in the micro-environment (Müller and Meineke 2007). In response to increased chemokines and cytokines, the endothelium is activated, and the expression of the adhesion molecules is accelerated and causes the migration of immune cells to the region, particularly leukocytes (Wolf, https://www.uptodate.com/contents/radiation-dermatitis). Inflammation caused by the migration of immune cells increases the damage. In addition to these, stem cell loss due to RT negatively affects the skin's repair cycle (Hopewell et al. 2003). Histamine-like factors have shown increased capillary permeability and vasodilatation. With increasing RT fractions, cellular damage increases, and if there is not enough time for repair, the damage becomes more evident towards the last stages of treatment (Hopewell et al. 2003; Mendelsohn et al. 2002). Dry desquamation develops due to erythrocytes' extravasation, and dry desquamation is usually the first clinical manifestation of RD. When RT damage is present in the basal cells and glandular tissue, epididymal necrosis with fibrinous exudate may occur. This is called moist desquamation. Finally, necrosis and ulceration of deeper tissues can be observed (Wolf, https://www.uptodate.com/contents/radiation-dermatitis; Bernier et al. 2011).

Although dermal toxicity starts earlier in sensitive skin, it usually develops within 2–3 weeks (Collen and Mayer 2006; Frederick and Renato 2008). Dry desquamation starts in 3 weeks, nearly 30 Gy; moist desquamation starts in 4–5 weeks, nearly 45–50 Gy (Sourati et al 2018). In our study, in patients with grade 2/3 RD, the RD started at 20 Gy (range, 14–36); but in patients with grade 1 RD, the initial dose of RD was 32 Gy (range, 16–56) ($p = 0.018$). The earlier the skin toxicity, the greater the final RD severity.

The low hemoglobin level can increase the radiosensitivity of the skin due to impaired tissue oxygenation. A limited number of studies evaluating the relationship between hemoglobin and RD (Gangopadhyay et al. 2014; Henke et al. 2000). Gangopadhyay et al. investigated the association between hemoglobin and mucocutaneous side effects in 227 patients with cervical cancer. In the patients

receiving concurrent CT, patients with hemoglobin values of 12 or higher had a higher mucocutaneous side effect ($p = 0.001$). On the other hand, in the study of Henke et al., 60 patients with head neck disease, lower hemoglobin levels were found to decrease the risk of RD, but the difference was not statistically significant ($p = 0.08$). In our study, no relation is found between hemoglobin and ferritin levels and RD.

Folic acid and vitamin B12 are important factors in DNA metabolism. It is shown that folacin-containing creams improve skin conditions in patients receiving RT (Debowska et al. 2006). Our study did not demonstrate any relationship between blood folic acid and vitamin B12 levels and the timing and severity of RD.

Smoking is known to impair wound healing by cutaneous vasoconstriction. Similarly, it may be thought that it adversely affects RD development with a similar mechanism (Porock et al. 1998; Wolf, https://www.uptodate.com/contents/radiation-dermatitis). However, in our study, no significant relationship was found between smoking and RD.

Advanced age is a risk factor for RD because it disrupts skin turnover (Porock et al. 1998; Salvo et al. 2010; Pollock 1988). However, no significant relation was found between RD development and RD grade and age in our study.

Malnutrition can be considered as a risk factor for RD by similarly affecting wound healing and metabolism. There was no significant relationship between RD and nutritional factors such as albumin, folic acid, and B12, but our study showed no significant malnutrition.

DM is a risk factor for RD when it causes adverse effects such as macrophage dysfunction, prolonged inflammatory phases, susceptibility to infection, and wound healing disorder (Sourati et al. 2018; Salvo et al. 2010). In our study, plasma blood glucose and Hba1c (for DM patients) values were evaluated, but no significant relationship could be detected.

There was a relationship between total dose and RD in accordance with the literature. In addition, a clinical RD initiation dose was noted in our study. As a result, as the initial dose of RD decreases, grade 2/3 significantly increases the risk of RD.

There are some limitations to our study. The number of patients is small, and the study is not randomized and is a single center. RT areas and treatment doses are not homogeneous.

Randomized evaluation of patient groups with more similar treatments to detect factors predicting the development of RD will contribute more.

Conclusion

There was no significant relationship between RD and hematological parameters in our study group. The severity of RD was associated with recurrent surgical intervention, RT total dose, and early onset of RD.

Declarations

Ethical Approval

All procedures performed in studies involving human participants were by the institutional and/or national research committee's ethical standards; and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Institutional Review Board approval was obtained for this study. The study was approved by the Ethics Committee of Ankara Atatürk Training and Research Hospital in February 2016.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Authors' Contribution

GAI: Conceived of or designed study, performed research, analyzed data, writing—original draft. AA: Conceived of or designed study, performed research, writing—review & editing. IPA: Conceived of or designed study, contributed new methods or models, writing—review & editing. SAA: Conceived of or designed study, contributed new methods or models, writing—review & editing.

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Figures

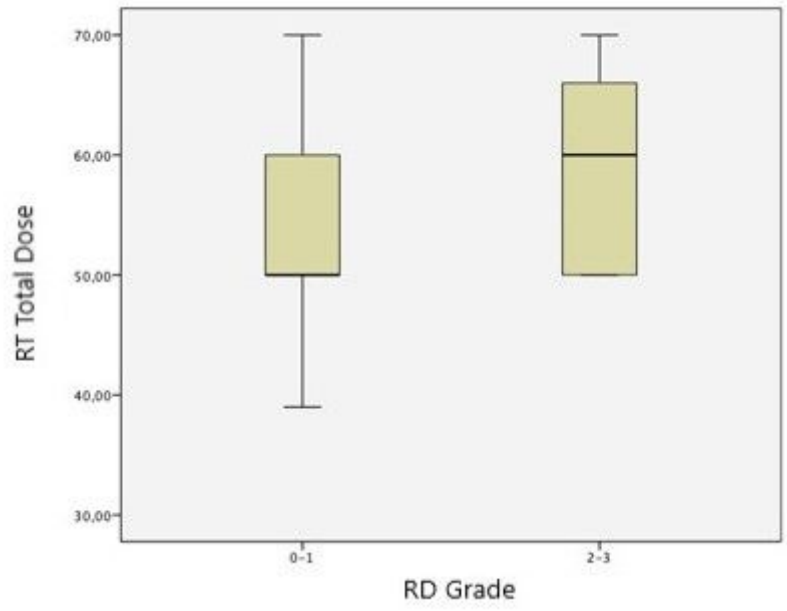

Figure 1

The risk of RD increases as the total dose of RT increases

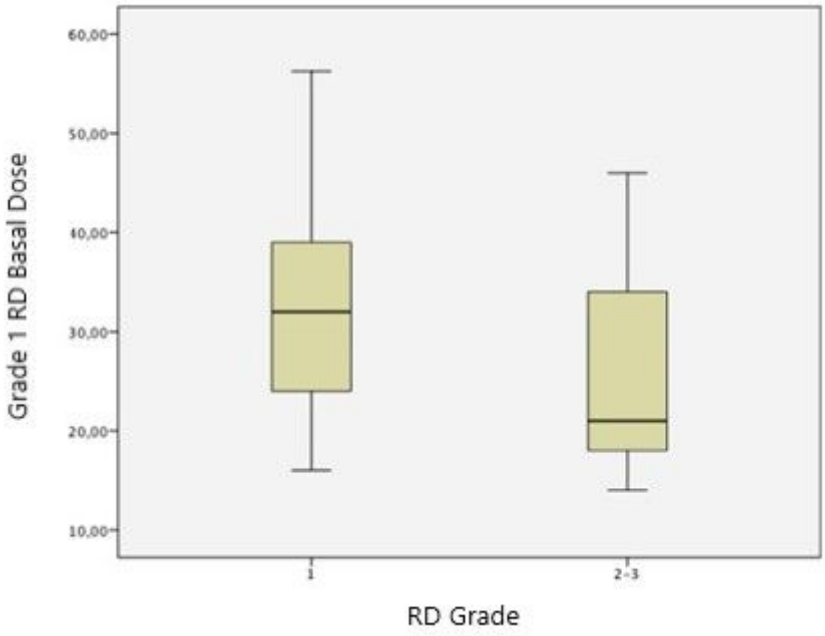

Figure 2

Relationship between the grade of RD and initial RT dose