BIOSCIENCE JOURNAL

ASSOCIATION OF SKIN TEMPERATURE, CUMULATIVE DOSE OF RADIATION, AND THE DIAGNOSIS OF RADIODERMATITIS

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How to cite: SHIGUIHARA, D. S. I., ULBRICHT, L. and NEVES, E.B. Association of skin temperature, cumulative dose of radiation, and the diagnosis of radiodermatitis. *Bioscience Journal*. 2025, **41**, e41001. https://doi.org/10.14393/BJ-v41n0a2025-67340

Abstract

Radiotherapy is one of the treatments of cancer, and radiodermatitis is one of the side effects, with a negative impact on the patient's quality of life, which can lead to limitation dose of radiation, delay in completion, or discontinuation of treatment. Recent studies show evidence that thermography can be useful in this context of radiodermatitis, as it is a technology that has been improved, there are still few studies showing thermal response and mapping of radiation dermatitis. This study analyzed the association between skin temperature, cumulative radiation dose, and the appearance of radiodermatitis. The research was carried out with 76 participants with skin, head or neck cancer and thermographic recording immediately before and after irradiation. The Radiation Therapy Oncology Group scale was used to diagnose radiodermatitis. As the main results in our sample, 70% of the participants had some degree of radiodermatitis, and significant differences in skin temperature were observed when compared to participants without (32.88 °C) and with radiodermatitis (thermal difference in average temperature greater than 1.0 °C for both grade I and grade II radiodermatitis). The ideal time for thermographic evaluation would be after receiving the daily dose, where we found a moderate correlation (0.474) between the temperature of the affected side after irradiation and the pre-irradiation cumulative dose. Our results demonstrate that radiodermatitis change skin temperature and thermographic analysis can quantify. Finally, to improve early diagnosis, we recommend that scales be constructed with greater definitions for the classification of radiation toxicity, without overlapping symptoms, considering quantitative criteria.

Keywords: Cancer. Infrared Thermography. Radiodermatitis. Radiotherapy.

1. Introduction

Cancer is a disease involving multifactorial aspects (genetic, environmental, and/or lifestyle factors), with a high incidence in Brazil and the world (Brasil 2020; Brasil 2022). The latest world estimate pointed to an increase of 2.1 million cases in the Americas alone by 2030 (OPAS 2020).

Radiotherapy is one of the available therapeutic modalities, which will be used in more than half of all patients treated with cancer (Kiprian et al. 2022). Similar to other forms of treatment, radiation therapy can result in significant side effects during and/or after treatment completion. Among them, the most common is radiodermatitis (Behroozian et al. 2021; Zasadziński et al. 2022).

Several factors influence the toxicity of the treatment, such as the total dose, fractionation

regimen, volume of irradiated tissue, concomitant systemic therapy and comorbidities (Kiprian et al. 2022; Zasadziński et al. 2022).

However, studies have shown a high prevalence of 81.19% (Costa et al. 2019) that are likely to reach 99.4% (Cardozo et al. 2020). Since Brazil does not have an official notification source, it is difficult to characterize its incidence (Monteiro et al. 2020) correctly.

Thus, according to Bontempo et al. (2020), the onset of keratinocyte destruction predisposes to changes in the epidermis integrity and in the skin healing processes, manifested by erythema, xerosis, desquamation, pruritus, and hyperpigmentation. With the continuity of treatment, as a compensatory response, mitotic activity increases, but new cells are produced faster than old ones are eliminated, resulting in dry desquamation.

Despite the high precision of modern treatments, irradiation can affect healthy tissues beyond tumors. This is so because radiation therapy directly destroys cancer cells (as well as surrounding healthy tissue cells) by apoptosis through free radicals that damage deoxyribonucleic acid (DNA) (Brasil 2008; Kiprian et al. 2022). These free radicals also activate several cells signaling pathways, such as pro-cytokines and inflammatory cytokines, indirectly destroying basal epidermal cells; thus, these direct and indirect action pathways mainly affect cells with high mitotic capacity. Therefore, basal keratinocytes, hair follicle stem cells, and melanocytes are the cells most affected by radiation (Kiprian et al. 2022).

When exposure continues, the ability of the basal layer to produce new cells is reduced, which ultimately results in the detachment of the epidermis, the release of serous fluid, and the formation of moist vesicles, classified as moist desquamation. The condition progression can result in difficult-to-heal ulcers, hemorrhage, and radionecrosis (Zasadziński et al. 2022).

Despite lesions high prevalence and severity, no gold standards in managing radiodermatitis have been established, and the diagnosis is still based on qualitative scales, which are generally dependent on the professional's experience. For radiodermatitis, although widely used (Huynh-le et al. 2014; Maillot et al. 2018; Behrrozian et al. 2021; Zasadziński et al. 2022), the scales have shown low to moderate reliability (insufficient validity and agreement).

Late diagnosis can interfere with the patient's quality of life and the success of the treatment since, in more severe cases, limitation of the therapeutic dose of radiation, delay in completion, or even suspension of radiotherapy may occur (Bontempo et al. 2020; Behrrozian et al. 2021).

Clinical research is in constant development, and recent studies have shown that thermography could be used to detect radiodermatitis (Maillot et al. 2018; Park et al. 2022). Thermography has been continuously improved and is widely used in biomedical research, as it allows tracking the inflammatory process by mapping the infrared radiation emitted by anybody at a temperature above absolute zero, but emitting any radiation, being non-invasive, portable, and easy to handle (Maillot et al. 2018; Verstockt et al. 2022).

Although the pathophysiology of radiodermatitis is known, few studies still relate infrared thermography to radiodermatitis (with their respective grading) according to the different irradiated areas.

Thus, the in-depth knowledge of thermal response to radiotherapy can be useful for the development of consensus and recommendations, both for early diagnosis and for a more objective quantitative assessment of the effectiveness of the treatments used. Aiming to contribute to this approach, this study analyzed the association of skin temperature, cumulative radiation dose, and the appearance of radiodermatitis.

2. Material and Methods

This is a prospective, cross-sectional study carried out in a unicentric field (reference hospital for cancer in the state). After approval by the Research Ethics Committee (# 4.323.201), data collection was carried out with 76 participants in the Radiotherapy sector between October/2021 and January/2022.

The inclusion criteria were: age above 18 years, having cognitive autonomy, and being on treatment for skin, head, or neck cancer.

The investigators did not interfere with the definition of the intervention or the irradiation planning. Thus, regarding the intervention, patients who received only radiotherapy and those who

received radiotherapy and chemotherapy were included. Regarding treatment planning (how the irradiation beam was applied according to the tumor topography), patients with 2D or 3D therapy were included.

Data acquisition

To collect data on the irradiated area, history taking, verification of the electronic medical record (to obtain treatment criteria), and a clinical evaluation of the treated skin were performed, based on the scale of analysis of irradiated structures developed by the RTOG (Radiation Therapy Oncology Group), to check for symptoms and signs of acute radiodermatitis, and if so, classify the lesion (Cox at al. 1995; Zasadziński et al. 2022) .

The classification ranges from grade O (zero) to IV (four), with 0 (zero) being no change from the baseline; grade I, presence of mild erythema, epilation, dry desquamation, and/or decreased sweating; grade II, tender (painful) or shiny erythema, moist or irregular desquamation, and/or moderate swelling; grade III, confluent moist desquamation (other than skinfolds) and/or significant swelling; and in the last scale, grade IV, the presence of ulceration, hemorrhage and/or necrosis (Zasadziński et al. 2022).

Care before evaluations involved: avoidance of topical agents in the head and neck region and use of a hair dryer; non-smoking; avoidance of hot baths or showers less than two hours before the exam; intake of only small portions of food four hours before the examination (Costa et al. 2013; Moreira et al. 2017, Salamunes et al. 2017).

Patients were instructed to arrive 15 minutes before the procedure for acclimatization purposes and to remain in the waiting room, whose temperature was maintained the same as that in the irradiation room (20.54±0.57 ºC). Air relative humidity was 56.1±4.84%. Upon entering the radiotherapy room to irradiate, the local professionals positioned the participant on the irradiation stretcher, according to the planning of each treatment. FLIR T540 Professional Thermal Camera (Flir Systems®, USA) was positioned on a tripod, one meter from the participant (Figure 1). Irradiation time ranged from 2 to 8 minutes. Images were captured immediately before and after irradiation. Images were recorded on the affected and contralateral sides.

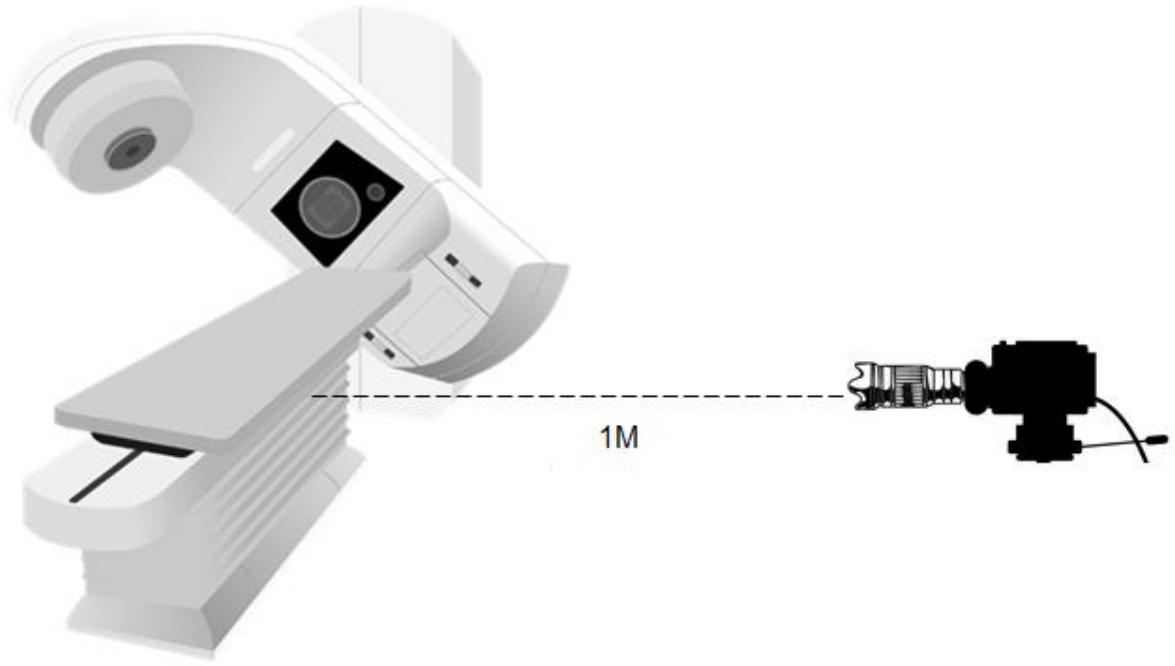

Figure 1. Illustration of thermal images acquisition.

Data analysis

Data collected were recorded in Microsoft Excel® and later inserted into the software *IBM SPSS 25.0* for analysis with a significance level of 0.05 (5%).

The thermal images were visualized in the Flir Tools® software, whose analysis was supported by the ellipse tool to delimit the region of interest (ROI). The minimum, mean, and maximum temperatures were identified for each ROI in the lava color palette.

Shapiro-Wilk test was applied to verify data distribution. Subsequently, descriptive statistics with measures of position and dispersion was used to analyze the correlation between the variable's degree of radiodermatitis and the cumulative irradiation dose. Wilcoxon and Mann-Whitney Tests were used to compare average temperatures within the evaluation moments and the impaired and contralateral sides. Kruskal Wallis test with Mann Whitney post hoc was also applied to compare the mean irradiation dose with the degree of radiodermatitis. Finally, the Spearman Test was applied to analyze the correlation coefficient (weak, moderate, and strong). Correlations below 0.4 were considered weak; between 0.41 and 0.75, moderate; and above 0.76, strong.

3. Results

Sample characterization

The sample consisted of 76 participants, with 60 men (79%) and 16 women (21%). Among them, 49 participants (64%) had comorbidities such as hypertension, diabetes, among others.

Among the participants, 53 (70%) had some sign of radiodermatitis, and the median daily dose of treatment was 212 (cGy), as shown in Table 1, which provides additional information on the characterization of the sample. In other words, the prevalence of radiodermatitis was 70%.

Table 1. Characterization of the sample of cancer participants who received radiotherapy.

Variable	Radiodermatitis	N	Median	25th	50th	75th
Age (years)	No	23	59	54.50	59.00	67.00
	Yes	53	62	55.00	62.00	69.00
Height (m)	No	23	1.62	1.57	1.62	1.69
	Yes	53	1.67	1.60	1.67	1.70
Weight (Kg)	No	23	59.50	49.75	59.50	72.20
	Yes	53	67.80	58.30	67.80	81.30
Body Mass Index (BMI)	No	23	21.48	17.26	21.48	27.14
	Yes	53	25.21	21.33	25.21	28.47
Daily Dose (cGy)	No	23	212	212.00	212.00	275.00
	Yes	53	212	200.00	212.00	212.00
Central Temperature (°C)	No	23	36.10	35.75	36.10	36.40
	Yes	53	36.10	35.90	36.10	36.20

Regarding radiotherapy, five models of linear accelerators were identified: CX; IX; 600#3; 2100; and 600#0. In addition, two types of energy were used in radiation applications, photons, and electrons, in an intensity varying between 6 MeV and 9 MeV for electron energy and 6 MV for photon energy.

Five types of oncological histology were identified among the participants: squamous cell carcinoma, basal cell carcinoma, poorly differentiated carcinoma, glioblastoma, and Kaposi's sarcoma, and 24 different points were irradiated. Among the participants, 59 (78%) had cancer in the head or neck region, and 17 (22%) had non-melanoma skin cancer (as shown in Table 2). As for the surgery to remove the tumor, 26 (34%) participants had already undergone the procedure.

All participants with head and neck cancer received treatment with photon energy with an intensity of 6 MV (Table 2), and grade I radiodermatitis was identified from the mean accumulation of 1908 cGy (tenth radiotherapy session).

Most participants with non-melanoma skin cancer (10-59%) received the treatment with electron energy at an intensity of 6 MeV (Table 2). In the others, the intensity was 9 MeV.

Table 2. Presentation of radiodermatitis according to the region treated, surgery to remove the tumor, concomitant treatment and radiation intensity.

Cancer region	N	Presence of Radiodermatitis N (%)	Degree of Radiodermatitis N (%)	Post-surgery N (%)	Concomitant chemotherapy N (%)	Intensity (MeV) N (%)
Head and neck	59	45 (76%)	I - 38 (64%) II - 7 (12%)	16 (27%)	27 (46%)	6 Mev - 59 100%
Non-melanoma skin	17	8 (47%)	I – 5 (29%) II – 2 (12%) III – 1 (6%)	10 (59%)	0 (0%)	6MeV - 10 (59%) 9MeV - 3 (18%)

Analysis of the influence of temperature on the degree of radiodermatitis according to a qualitative classification

As for the influence of radiation from the skin temperature on the affected side for grade I radiodermatitis (Figure 2), it was possible to find a significant difference both in the temperatures immediately before and after irradiation when compared with participants without radiodermatitis. However, for grade II radiodermatitis (Figure 3), the ideal time for diagnosis would be post-irradiation, and only maximum or mean temperatures should be considered (Table 3).

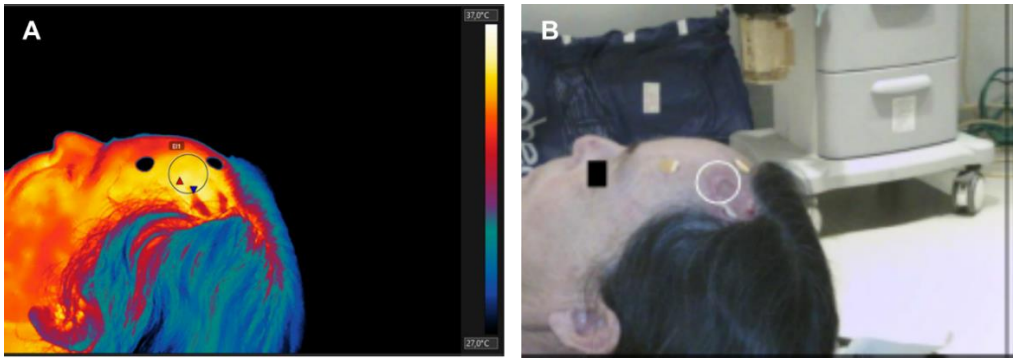

Figure 2. A - Thermogram and B - photograph before irradiating the primary focus of the tumor (accumulated dose at 2475cGY) – Grade I radiodermatitis characterized by mild erythema.

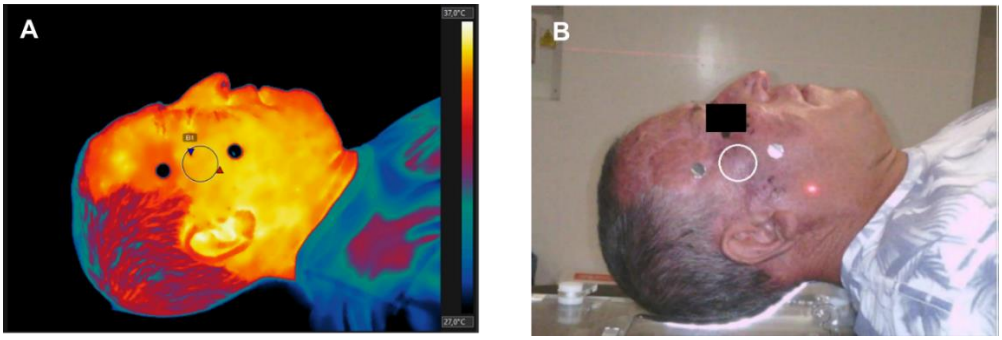

Figure 3. A - Thermogram and B - photograph before irradiating the primary focus of the tumor (cumulative dose at 3300cGY) - grade II radiodermatitis characterized by erythema and moderate edema.

As for the differentiation between the degrees of radiodermatitis (Table 3), following the classification between grades I and II recommended by the qualitative scale, it was impossible to visualize a significant difference through the thermal analysis or the average cumulative dose. The mean cumulative radiation dose in the pre-irradiation tumor area was significantly different ($p < 0.05$) for those who did not have radiodermatitis (grade 0= 2295 cGY) compared to those who had the diagnosis.

However, there was no significant difference between the grades classifying the severity of symptoms - grade I (4047 cGY), grade II (5011 Cgy), or grade III (3800 cGY) - with only one case.

Table 3. Skin temperature profile before and after irradiation of the daily dose according to the clinical diagnosis of the radiodermatitis grade in the tumor area.

	GRADE OF RADIODERMATITIS		
	No Radiodermatitis	I	II
	Mean (°C)	Mean (°C)	Mean (°C)
ALE Maximum	33.56[a]	34.85[b]	34.73[a,b]
ALE Mean	32.88[a]	34.17[b]	33.93[a,b]
ALE Minimum	32.09[a]	33.52[b]	33.07[a,b]
DLE Maximum	33.55[a]	35.23[b]	35.19[b]
DLE Mean	32.93[a]	34.72[b]	34.70[b]
DLE Minimum	32.24[a]	34.15[b]	33.87[a,b]

ALE = Affected Side Temp. Before Irradiation; DLE = Affected Side Temp. After Irradiation
Note: Values in the same row and subtable that do not share the same subscript ([a] or [b]) are statistically different ($p < 0.05$) in the two-step equality test for column means.

Thermal analysis of participants with head and neck cancer with irradiation in the 3d plane

In this subgroup of 59 participants, irradiation was performed both in the primary focus of the tumor and adjacent areas (thus, the contralateral side also received some degree of irradiation).

Table 4 compares the affected side (primary focus of radiation) with the contralateral side (secondary focus). Data show that radiation impacts the temperature of the irradiated area and that, as expected, temperatures on the affected side (maximum, mean, or minimum) are significantly higher than those on the contralateral side, either immediately before or after irradiation. Remember that, as shown in Table 2, 26 (34%) participants had already undergone surgery to remove the tumor.

Table 4. Comparison of skin temperatures between the affected and contralateral sides, at each moment of evaluation. Bilateral irradiation (N = 59).

Moment	Side and Temperature	Mean (°C)	Standard deviation	p value (Wilcoxon)
Before irradiation	ALE Maximum	34.65	1.26	0.010
	ALC Maximum	34.33	1.17	
	ALE Mean	34.02	1.51	0.001
	ALC Mean	33.66	1.34	
	ALE Minimum	33.49	1,68	<0.001
	ALC Minimum	33.05	1.45	
After irradiation	DLE Maximum	35.01	1.13	0.006
	DLC Maximum	34.72	1.09	
	DLE Mean	34.53	1.18	<0.001
	DLC Mean	34.17	1.23	
	DLE Minimum	34.05	1.37	<0.001
	DLC Minimum	33.61	1.33	

ALE = Affected Side Temp. Before Irradiation DLE = Affected Side Temp. After Irradiation ALC = Contralateral Side Temp. Before Irradiation DLC = Contralateral side Temp. after irradiation.

When comparing the moments immediately before and after irradiation, on both sides (affected and contralateral), the temperatures (maximum, mean, and minimum) after irradiation are significantly higher than before receiving a new dose of treatment, as expected, once both receive the treatment (Table 5).

Thermal analysis of participants with non-melanoma skin cancer with 2D plane irradiation

In this case, participants are irradiated only on the affected side.

Table 6 compares the affected side (the primary focus of radiation) with the contralateral side (which did not receive radiation). This time, there is a significant difference in the mean and maximum temperatures only after irradiating the affected side.

Table 5. Comparison of skin temperatures among the evaluation moments, at each side evaluated (affected and contralateral). Bilateral irradiation (N = 59).

Moment	Side and Temperature	Mean (C°)	Standard deviation	p value (Wilcoxon)
Affected side	ALE Maximum	34.55	1.26	<0.001
	DLE Maximum	34.96	1.17	
	ALE Mean	33.89	1.50	<0.001
	DLE Mean	34.49	1.21	
	ALE Minimum	33.32	1.71	<0.001
	DLE Minimum	34.00	1.41	
Contralateral Side	ALC Maximum	34.27	1.20	<0.001
	DLC Maximum	34.70	1.14	
	ALC Mean	33.58	1.36	<0.001
	DLC Mean	34.16	1.28	
	ALC Minimum	32.96	1.47	<0.001
	DLC Minimum	33.61	1.38	

ALE = Affected Side Temp. Before Irradiation DLE = Affected Side Temp. After Irradiation ALC = Contralateral Side Temp. Before Irradiation DLC = Contralateral side Temp. after irradiation.

Table 6. Comparison of skin temperatures between the affected and contralateral sides at each moment of evaluation. Unilateral irradiation (N = 17).

Moment	Side and Temperature	Mean (C°)	Standard deviation	p value (Wilcoxon)
Before irradiation	ALE Maximum	33.80	2.69	0.053
	ALC Maximum	32.75	1.78	
	ALE Mean	32.89	2.59	0.069
	ALC Mean	31.77	1.90	
	ALE Minimum	31.57	2.59	0.055
	ALC Minimum	30.50	2.11	
After irradiation	DLE Maximum	33.78	2.85	0.044
	DLC Maximum	32.98	2.14	
	DLE Mean	33.01	2.96	0.019
	DLC Mean	31.86	2.18	
	DLE Minimum	31.75	3.19	0.148
	DLC Minimum	30.55	2.73	

ALE = Affected Side Temp. Before Irradiation DLE = Affected Side Temp. After Irradiation ALC = Contralateral Side Temp. Before Irradiation DLC = Contralateral side Temp. after irradiation.

Despite all temperatures on the affected side being higher than those on the contralateral side at all times, this subgroup consists of only 17 people, which may explain the lack of statistical significance in minimum temperatures and between immediately pre-irradiation temperatures.

Table 7. Comparison of skin temperatures among the evaluation moments on each side evaluated (affected and contralateral). Unilateral Irradiation (N = 17).

Moment	Side and Temperature	Mean (C°)	Standard deviation	p value (Wilcoxon)
Affected side	ALE Maximum	33.80	2.69	0.191
	DLE Maximum	33.58	2.98	
	ALE Mean	32.89	2.59	0.691
	DLE Mean	32.81	3.10	
	ALE Minimum	31.57	2.59	0.865
	DLE Minimum	31.61	3.33	
Contralateral side	ALC Maximum	32.86	1.78	0.569
	DLC Maximum	32.99	2.21	
	ALC Mean	31.93	1.94	0.877
	DLC Mean	31.84	2.25	
	ALC Minimum	30.71	2.19	0.691
	DLC Minimum	30.47	2.79	

ALE = Affected Side Temp. Before Irradiation DLE = Affected Side Temp. After Irradiation ALC = Contralateral Side Temp. Before Irradiation DLC = Contralateral side Temp. after irradiation.

When comparing the pre and post-irradiation moments (Table 7), on both sides (affected and contralateral), right after irradiation, it appears that there is no statistical difference between temperatures (maximum, mean, or minimum).

Correlation analysis between intrinsic and extrinsic factors and thermal data in the appearance of radiodermatitis

Correlations referring to intrinsic (Age, BMI-Body Mass Index, and degree of radiodermatitis), extrinsic (cumulative dose, pre-radiation dose, daily dose), and thermal (temperatures: on the affected side before radiation (ALE); on the affected side after radiation (DLE) and the delta of the affected side (difference between the mean temperatures before and after irradiating)) factors are shown in Table 8.

Weak correlations were obtained between the delta of the temperature of the affected side and age (0.355), ALE with the pre-irradiation dose (0.332), and between the daily dose and the BMI.

Table 8. Correlation between the degree of radiodermatitis, thermal, extrinsic and intrinsic factors.

	Degree of radiodermatitis	Age	BMI	Daily dose (cGY)	Pre-irradiation dose (cGY)	Mean ALE (ºC)	Mean DLE (ºC)	Delta affected side
Degree of radiodermatitis	1.000	0.055	0.176	-0.238*	0.562**	0.202	0.325**	0.220
Age		1.000	0.411**	0.209	0.012	0.052	0.263*	0.355**
BMI			1.000	0.365**	-0.020	-0.217	-0.028	0.257*
Daily dose (cGY)				1.000	-0.205	-0.155	-0.058	-0.035
Pre-irradiation dose					1.000	0.332**	0.474**	0.251*
ALE_MEAN						1.000	0.819**	-0.301*
DLE_MEAN							1.000	0.189
Delta affected side								1.000

* *p<0.001; ALE = Affected Side Temp. Before Irradiation DLE = Affected Side Temp. After Irradiation.

Meanwhile, mean correlations were found between the dose immediately pre-irradiation and the degree of radiodermatitis (0.562) and DLE with the dose immediately before irradiation (0.474).

4. Discussion

Symptoms of radiodermatitis are generally associated with discomfort, skin burning, itching, and pain that have a negative impact on the patient's quality of life (Spasić et al. 2018; Kiprian et al. 2022). In addition, changes in body image, anxiety and depression, and anxiety symptoms can also occur, which add to the impact generated by cancer, mainly impacting quality of life domains of physical and cognitive function (Cardoso et al. 2020).

The study by Bontempo et al. (2020) claims to be the first Brazilian study to perform this estimate in cancer patients undergoing radiotherapy. The study followed 112 participants, and the incidence ranged from 48% to 100%. The highest incidence was precisely that reported to participants with head and neck cancer (which represented 31 people in the sample).

Regarding intrinsic risk factors for the development of radiodermatitis, 60% of our participants reported some comorbidity but did not present advanced age or changes in BMI (greater than 25 or very low, demonstrating low nutritional status).

Kiprian et al. (2022) cite that the main intrinsic factors that can impact the development of radiodermatitis are being an older person, obese, and smoker. Regarding treatment-related extrinsic risk factors, such as dose fraction (< 200 cGY), total dose and the technique used are very important and can influence the severity of the skin reaction (Kiprian et al. 2022). In our study, the median daily dose was 212 cGY.

Moreover, concomitant treatment with chemotherapy may also develop more severe

radiodermatitis. In our sample, 46% of participants treated for head and neck cancer also received chemotherapy.

Authors describe that this occurs because the mechanism of action of systemic drugs is very similar to that of radiation, which ends up sensitizing skin cells (Kiprian et al. 2022). For example, authors such as Bernier et al. (2008) found that patients receiving cetuximab (concurrently with radiation therapy for locally advanced head and neck cancer) had pathophysiological and clinical characteristics that differ from the others. This was because the systemic administration of this EGFR (Epidermal Growth Factor Receptors) inhibitor resulted in an upregulation of the growth inhibitor $p27.^{kip}$ in keratinocytes, compromising cell differentiation and growth.

Regarding the influence of temperature on the degree of radiodermatitis according to the qualitative classification, few studies have been published in this regard because only in recent years, with the improvement of technology, have researchers become interested in the technique again, which has been showing promising results in the most diverse fields (Maillot et al. 2018; Verstockt et al. 2022).

In our study, it was possible to observe significant differences in skin temperature, comparing participants with and without radiodermatitis. Participants with radiodermatitis arrived for treatment with a thermal difference in average temperature greater than 1.0 °C. Data also showed a moderate correlation (0.474) between the mean temperature of the affected side immediately after irradiation and the pre-irradiation dose.

Maillot et al. (2018) also describe that, in their study, a remarkable temperature increase was observed during radiotherapy in all participants. The authors suggest that with a threshold of 1.4°C of difference defined in advance between the irradiated and healthy breast, it would be possible to anticipate the occurrence of radiation-induced radiodermatitis (with positive and negative predictive values of 70% and 77%, respectively).

In our study, when thermographic evaluation is performed before treatment with the new daily dose, the correlation drops to 0.332. We also found a mean correlation between the pre-irradiation dose and the degree of radiodermatitis (0.562).

A study by Sekine et al. (2000) following nine cases undergoing treatment for breast cancer obtained the same result describing significant thermal differences ($p<0.01$) at the time before radiation between the healthy side (34.1 °C +/- 1.5) and the affected side (35.2 °C +/-0.6).

Erythema, the initial symptom of radiodermatitis, is dose-dependent and may be asymptomatic. It results from the imbalance between anti- and pro-inflammatory processes (Kiprian et al. 2022), which results in the obliteration of arterioles (Spasić et al. 2018). Clinically, the skin becomes swollen and hot, evidenced in the thermographic analysis.

Grade I radiodermatitis and erythema are also followed by epilation. Depigmentation may occur, and the process of dry desquamation begins, which develops as a result of the reduction of the active layer of the epidermis (generally in the second week of radiotherapy). This generates a division in the surviving cells (which occurs between the second and fourth week of radiotherapy). The clinical manifestation is itching and skin desquamation (Spasić et al. 2018).

Between the fourth or fifth week of treatment, the symptomatology of grade II usually begins, where the erythema becomes painful, the edema is moderate, the pruritus increases, and the dry desquamation progresses to moist desquamation (kiprian 2022). Moist desquamation develops due to damage to the basal layer, with damage to vascular elements allowing fluid to diffuse from the dermis capillaries to the skin surface (Spasić et al. 2018). Skin pigmentation may also occur due to melanin production by melanocytes (Spasić et al. 2018).

This is a transitional phase, where some symptoms overlap, which in our work cannot be differentiated from grade I either through thermographic analysis or the mean cumulative dose analysis.

Vascular changes occur between one phase and another and are quantitatively measured by thermographic analysis and by the sum of doses already received (accumulated), occurring at a time different from that of visualization of a particular symptom when it is effectively classified on the visual scale.

Regarding qualitative scales, Behrrozian et al. (2021) describe that despite the high prevalence of radiodermatitis, there is limited consensus due to the lack of standardization among the instruments used

and that, for this reason, there is no single instrument considered the “gold standard”. In their research, the assessment instruments (scales) normally used showed insufficient reliability, validity, and agreement (minimum to moderate effectiveness).

Years earlier, this same problem had already been addressed in the study by Huynh-Le et al. (2014) in a survey of 250 oncologists to assess the NCI CTC and RTOG late toxicity scales after prostate radiotherapy. The authors showed moderate agreement when using the NCI CTC scale (ICC=0.52) and only fair agreement using the RTOG (ICC=0.28). The conclusions recommend that clearer definitions for toxicity classification shall be constructed.

As for the other degrees of the scale, grade III is described by confluent moist desquamation, pigmentation, and edema, and grade IV by the presence of ulceration, hemorrhage and/or necrosis (Kiprian et al. 2022; Zasadziński et al. 2022). These phases were not analyzed. This study had only one case of grade III radiodermatitis and none of grade IV.

Spasić et al. (2018) describe that ulceration and necrosis are rarer events and generally occur after re-irradiation due to infection of vascular elements and connective tissue damaged by radiation.

However, from grade III onwards, the continuity of treatment is dependent on a medical opinion when, in general, treatment is interrupted until the lesion has reduced or healed completely. This interruption can reduce cure rates and serve as a predictive factor for late reaction with fibrosis (Bontempo et al. 2020; Cardoso et al. 2020).

On the other hand, a study by Sekine et al. (2020) with 43 participants undergoing treatment for breast cancer, using the CTCAE 4.0 scale (National Cancer Institute Common Terminology Criteria for Adverse Events), found that quantitative measurements detected the effects of irradiation earlier than qualitative indices. However, evaluating the specific symptoms of radiodermatitis, qualitative and quantitative assessments showed similar time courses and peak periods. In these authors’ study, determining correlations between qualitative and quantitative values was an important objective. They describe a moderate correlation of the CTCAE score for the presence of erythema in 5 weeks of irradiation and a weak correlation of the degree of erythema (limitation as to judgment of symptom severity) at the same time.

Thus, regardless of whether a quantitative or qualitative scale is used, it is important to focus on diagnosis in the early stages of radiodermatitis to avoid its progression and treatment interruption.

Concerning participants with cancer in the head and neck region with irradiation in the 3D plane, we followed 59 participants, and of these, 64% developed grade I and 12% grade II radiodermatitis.

The study by Bontempo et al. (2020) describes that all 31 participants followed up had some degree of radiodermatitis throughout treatment, with a mean time for the first occurrence of the event of 11 days. Regarding the classification, only one participant had been diagnosed with grade III radiodermatitis.

The thermal analysis of our study showed that the radiation impacted the temperature of the irradiated area and that, as expected, the temperatures on the affected side were significantly higher than those on the contralateral side. All our participants were irradiated using photon energy with an intensity of 6 MV, fractionating the total dose between 30 to 35 sessions.

Depending on the total dose, some authors recommend fractionation into up to 30 doses, as in the study by Petkar et al. (2016), who focused on dysphagia (another side effect that can come from radiotherapy).

As for the incidence of radiodermatitis, a study by Cardoso et al. (2020) with 167 participants showed that 99.6% had it (64.7% with grade I, 23.4% with grade II, and 11.4% with grade III). The authors found no significant association between sociodemographic characteristics and comorbidities (separately). When they associated hypertension and diabetes, they found a four-fold relative risk of developing radiodermatitis. The higher prevalence in this study may have occurred due to the use of the 2D technique (as these participants had a six-fold greater relative risk of developing severe radiodermatitis).

As for participants with Non-Melanoma Skin Cancer with Irradiation in the 2D Plane, our group consisted of only 17 people (47% developed radiodermatitis), who all had non-melanoma skin cancer.

Skin cancer is the most prevalent type in humans and refers to a series of pathological entities originating from various cells of the epidermis and dermis, being subdivided mainly into melanoma and non-melanoma (Verstockt et al. 2022; Zelin et al. 2021). These authors also describe effective treatments

that often have less impact on patient's quality of life; therefore, screening is recommended for moderate to high-risk populations.

As for the thermal analysis, despite all temperatures on the affected side being higher than those on the contralateral side at all times, we found a significant difference in mean and maximum temperatures only after irradiating the affected side. This may have occurred due to the small sample size.

For this group, radiotherapy was applied with electron energy at an intensity of 6 MeV (59%) and 9 MeV (18%), with a total dose of 3300 cGy and 6000 cGy, distributed between 10 to 20 sessions.

Thus, our sample presented a higher total dose at 500 cGy than in the study by Zaorsky et al. (2017), who describe the final dose of 5500 cGy distributed between 10 to 20 sessions.

As for the limitations, our study was carried out during the COVID-19 pandemic, and due to the restrictions imposed, its design was changed from longitudinal to cross-sectional, so it was not possible to evaluate the participants before they started treatment and follow them until the end (which could impact the presentation of a greater number of participants with symptoms or more severe symptoms). Likewise, the pandemic negatively impacted our sample size, resulting in smaller groups than anticipated. Finally, the same person performed all the assessments, so the qualitative scale was used without the inter-rater assessment.

5. Conclusions

The present study concluded, through thermal analysis, that there are significant differences in skin temperature when comparing patients without (32.88°C) and with radiodermatitis (thermal difference in mean temperature greater than 1.0°C, both for subjects classified in grade I as for those classified in grade II). In other words, radiodermatitis promotes changes in skin temperature, and thermographic analysis can quantify it.

Regarding the diagnostic process using the thermographic resource, it is suggested that the ideal time to conduct the evaluation is after receiving the new daily dose due to the moderate correlation (0.474) between the temperature of the affected side after irradiation and the pre-irradiation accumulated dose.

Finally, the present study reinforces the need to develop a new clinical classification based on mathematical values, not just symptomatological and visual ones, as is the current methodology for diagnosing radiodermatitis.

Authors' Contributions: All authors cited in this manuscript contributed to the design process, acquisition, analysisand interpretation of data, writing of the article, critical review of important intellectual content and final approval of the version to be published.

Conflicts of Interest: The authors declare no conflicts of interest.

Ethics Approval: Approved by Research Ethics Committee of Hospital Erasto Gaertner. CAAE: 38658920.3.0000.0098. Number: 4.323.201.

Acknowledgments: I declare for all due purposes that the research entitled "THERMOGRAPHY AS SUPPORT FOR THE DIAGNOSIS OF RADIODERMITIS" will not entail costs for the research participant, for the Erasto Gaertner Hospital (if applicable), for the Unified Health System (SUS) or operators of health. We declare that the costs of procedures and imaging exams, carried out for the sole purpose of research, will be the responsibility of researcher Dryelle Soster Iede Shiguihara.

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Received: 25 December 2022 | **Accepted:** 14 August 2023 | **Published:** 7 February 2025