

Radiodermatitis: Analysis of Predictive Factors in Breast Cancer Patients

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Radiodermatites: Análise dos Fatores Preditivos em Pacientes com Câncer de Mama

Radiodermatitis: Análisis de Factores Predictivos en Pacientes con Cáncer de Mama

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Abstract

Introduction: Radiotherapy is one of the therapeutic modalities chosen for adjuvant and neoadjuvant treatment in patients with breast cancer. This modality causes a painful skin reaction known as radiodermatitis. **Objective:** To evaluate the factors related with the appearance of radiodermatitis after radiotherapy and their relationship with the highest degree of toxicity in patients with breast cancer. **Method:** Retrospective study, with 117 patients with breast cancer submitted to 3D conformational radiotherapy between 2016 and 2018, at variable doses. Personal data were collected from medical records, and the degree of radiodermatitis established according to the criteria of the Radiation Oncology Group. The total of 15 predictive factors in potential were listed and later analyzed by univariate and multivariate statistics. **Results:** The study population presented an average of 50 years, 47% reported some comorbidities, 59.83% underwent radical surgery and 81.19% developed radiodermatitis. In a multivariate analysis, there was an association between development of radiodermatitis and higher doses of radiation ($p=0.011$) and daily bolus use ($p=0.009$). **Conclusion:** The main elements that culminated in higher degrees of radiodermatitis were the dose of radiation and the use of daily bolus. By categorizing the predictive factors, we can identify the patient with the highest risk of severe skin lesions and enables the creation of more effective protocols for the prevention of radiodermatitis.

Key words: Radiodermatitis; Breast Neoplasms; Acute Toxicity; Radiotherapy.

Resumo

Introdução: A radioterapia é uma das modalidades terapêuticas de escolha para os tratamentos adjuvante e neoadjuvante, em pacientes com câncer de mama. Tal modalidade provoca reação de pele dolorosa conhecida como radiodermatite. **Objetivo:** Avaliar os fatores associados com o aparecimento de radiodermite após radioterapia e a sua associação com o maior grau de toxicidade nesses pacientes. **Método:** Estudo retrospectivo, com 117 pacientes com de câncer de mama submetidos à radioterapia conformacional 3D, entre 2016 a 2018, em doses variáveis. Dados pessoais foram coletados a partir de prontuário, e o grau de radiodermite estabelecido segundo os critérios do grupo de oncologia radioterápica. O total de 15 potenciais preditivos foram elencados e analisados por estatísticas univariadas e multivariadas. **Resultados:** A população do estudo apresentou uma média de 50 anos, 47% relataram alguma comorbidade, 59,83% realizaram cirurgia radical e 81,19% desenvolveram radiodermite. Observou-se, em análise multivariada, associação do desenvolvimento de radiodermite com maiores doses da radiação ($p=0,011$) e com uso de bólus diário ($p=0,009$). **Conclusão:** As principais variáveis que culminaram em maiores graus de radiodermite foram a dose da radiação e o uso de bólus diário. Categorizando os fatores preditivos, identificam-se o paciente com maior risco de lesões graves e a possibilidade da criação de protocolos mais eficazes na prevenção das radiodermatites.

Palavras-chave: Radiodermatite; Neoplasias da Mama; Toxicidade Aguda; Radioterapia

Resumen

Introducción: La radioterapia es una modalidad terapéutica para tratamiento adyuvante y neoadyuvante, en pacientes con cáncer de mama. Tal modalidad provoca reacción de piel dolorosa conocida como radiodermatitis. **Objetivo:** Evaluar factores conexos con la aparición de radiodermatitis tras la radioterapia y su asociación con el mayor grado de toxicidad. **Método:** Estudio retrospectivo, con 117 pacientes con cáncer de mama sometidos a la Radioterapia Conformacional 3D entre 2016 a 2018. Los datos personales fueron recolectados a partir de prontuario, así como el grado de radiodermatitis establecido según los criterios del grupo de oncología radioterápica. El total de 15 potencial predictivos fueron enumerados y posteriormente analizados por estadística univariada y multivariada. **Resultados:** La población del estudio presentó un promedio de 50 años, el 47% informó de algunas comorbilidades, el 59,83% se sometió a cirugía radical y el 81,19% desarrolló radiodermatitis. En un análisis multivariado, hubo una asociación entre el desarrollo de radiodermatitis y dosis más altas de radiación ($p=0.011$) y el uso diario de bolos ($p=0.009$). **Conclusión:** Las principales variables que culminaron en mayores grados de radiodermatitis fueron la dosis de radiación y el uso de bolos diarios. Al categorizar los factores predictivos, podemos identificar al paciente con el mayor riesgo de lesiones cutáneas graves y permitir la creación de protocolos más efectivos para la prevención de la radiodermatitis.

Palabras clave: Radiodermatitis; Neoplasias de la Mama; Toxicidad Aguda; Radioterapia.

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INTRODUCTION

Breast cancer is the second world most frequent neoplasm and more common in women. The world estimation indicates an incidence of 1.7 million and, in Brazil, according to “Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA)” in 2018 and 2019, nearly 600 thousand new cases of cancer will occur, 60 thousand of which are primary breast cancer¹.

Among the therapeutic options for breast cancer treatment, radiotherapy can be utilized in post-operation/post-chemotherapy (adjuvant) to destroy remaining cells and reduce locoregional relapse or in pre-operation (neoadjuvant) prior to the principal modality of treatment to reduce the tumor and facilitate the operatory procedure².

Frequently this therapeutic modality provokes cutaneous toxicity more known as radiodermatitis. These dermatitis are injuries defined as a set of reactions resulting from the destruction of skin basal cells, caused by the exposure to the ionizing radiation required for radiotherapy³. Acute radiodermatitis onsets around the third week of treatment, can occur late after 90 days from the beginning of the treatment and, despite the efforts to minimize the total dose of the radiation, nearly 80-90% of the patients in radiotherapy treatment will develop this condition in some level, but it is estimated that only 10-15% in more advanced degrees (moist desquamation and ulceration)^{4,5}.

It is worth mentioning that the reactions of skin toxicity are painful, typically occur in folds as axillary, below breast and evolve as erythema, hyperpigmentation, dry and moist desquamation, the last characterized by exposure of the skin with exudate, ulceration and necrosis, eventually⁶. Scarring is damaged, further, by the inhibition of the normal granulation tissue, fibrogenesis and angiogenesis. Lymphedema is another radiotherapy-associated complication, affecting 25% of the patients, causing pain, tension and augmentation of the affected upper limb volume. Therefore, these are complex bruises associated to the quality of life of the patients in radiotherapy and may lead to systemic infections and permanent scars^{3,7,8}.

With the objective of evaluating the intensity and facilitate the design of protocols for the prevention and treatment of radiodermatitis, the *radiation therapy oncology group* (RTOG) developed the *acute radiation morbidity scoring criteria* – and classifying the effects of radiotherapy, which identifies scores 0 (no reaction); 1 (mild erythema, dry desquamation, epilation, diminished sudoresis); 2 (moderate brilliant erythema, exudative dermatitis in plates and moderate edema); 3 (exudative dermatitis beyond the

cutaneous folds and intense edema); and 4 (ulceration, hemorrhage, necrosis). The score of RTOG is the most utilized, accepted and recognized by medical communities and adopted extensively for more than 25 years³.

Several randomized studies evidenced variables associated with the risk and severity of radiodermatitis, associating them to radiation-related aspects (type of equipment), use of bolus (maleable material that boosts the dose at the surface of the entry of the field), homogeneity of the dose, volume irradiated and radiosensitivity of the tissue involved⁵.

It is believed that the inherent aspects of the patient, as age, tobacco addiction, nutritional status, preexisting chronic diseases and concomitant antineoplastic treatment can interfere in the skin reactions because of the alteration of the scar process. The size of the breast, the cancer staging according to the Classification of Malignant Tumors (TNM) and irradiated adjacent areas (axillary and skin folds) are important components for better skin reaction because they interfere in the amount of dose to be applied. A large breast, theoretically, receives the bigger dose in the skin to ensure the penetration in the tissues and deeper structures⁶.

In regard to radiodermatitis management, there are still controversies about the finality of the prevention of the skin reaction, relief of the symptoms or treatment in several products studied. There are recommendations about the use of camomile tea, essential fatty acids-based lotions or unsaturated fatty acids, hydrocolloid plate, *Aloe vera* and *Calendula officinalis* (phytotherapics). The technology of light as bio photomodulation has been proved a safe and effective method to improve the scarring of the wounds, regeneration of tissues, pain relief and inflammation. However, there is no consensus about the best treatment or form of prevention, not even a standard protocol for the institutions with few models being encountered and without efficacy literature-based evidence⁵.

The control of this disease continues to be a multidisciplinary effort of high relevance that focuses in the identification of high risk patients, classification of radiodermatitis, techniques of skin preservation and control of wounds, which, if ill-managed, may lead to temporary suspension of the radiotherapy and risk of failure of the therapeutic process; this also may imply in economic impact and survival. It is necessary to disseminate this theme nationally, as the majority of studies in this area is international with discrepant conclusions, subjective analyzes (as the size of the breast) and because the knowledge of this occurrence may determine policies and protocols of clinical practice and control of this radiotoxicity⁹.

Under this perspective, the present study evaluates objectively the possibly associated variables with the manifestation and severity of the post-therapy acute dermatologic injuries in oncology specialized services; the purpose is to encourage the elaboration of studies that validate the evidence of benefits of the existing preventive and therapeutic measures and the creation of new actions of prevention and a standard prophylactic protocol for radiotherapy sites in order to enhance more satisfactory oncologic treatments.

METHOD

An observational, analytic, quantitative-approach retrospective study was carried out with 117 patients enrolled, diagnosed with breast cancer who underwent radiotherapy treatment in a public and private oncology reference service. In the process, it were included all the patients with breast cancer radiotherapy treatment from January 2016 to January 2018 in any clinical staging and released upon conclusion of the radiotherapy. It were excluded the patients with incomplete treatment or submitted only to palliative radiotherapy (some cases of metastasis and/or anti-hemorrhage radiotherapy) because the dose of radiation is well below the therapeutic radiotherapy. The base was a population of 787 cases of cancer registered in the aforementioned period; from then on, 130 cases were selected classified as CID 10 C50 (breast cancer) and excluded 13 charts according to the criteria mentioned, resulting in 117 patients. The Institutional Review Board of “Universidade Federal do Maranhão” approved the study, report number 2474576.

The charts contained the identification of the patient, questionnaire of habits of life and previous treatments, report of the physician with cancer staging, radiotherapy form, week reports and treatment discharge. The factors evaluated were chosen after meeting with the physicians of the health facility, based in the experience at the service and what was found in the literature about the relation of alterations of the skin integrity and scar process that could interfere with the level of toxicity; these factors were related to the patient (age, habits of life, comorbidities, size of the breast and cancer staging) and to the oncologic treatment (chemotherapy, hormone therapy and previous radiation, previous surgery, dose of the radiation, dose fractioning, dose *boost*, use and size of the bolus).

The staging of the disease was analyzed and categorized according to the Sytem TNM of the *American Joint Committee on Cancer*, 7th edition, because the admission of the patient and classification was made in 2016 and 2017. The score of radiodermatitis was determined from

the weekly reports based in the RTOG Acute Toxicity Scoring Criteria and registered in the charts¹⁰.

The size of the breast was estimated for all the patients by the Department of Physical Medicine of the health facility utilizing the system Eclipse Planning (version 10.0, *Varian Medical Systems*, Palo Alto, CA[®]) with the software *External Beam Planning* where the contours are evaluated from a previous computed tomography as shown in Figure 1 and the distance of entry and exit of the field was limited (latero lateral distance) having as reference the central axis of the breast and ruler in centimeters.



Figure 1. Print screen of the method of calculation of the size of the breast based in the computerized tomography in the system Eclipse Planning. The distance of 19.97 cm is the size of the breast of this patient

The 3D conformational radiotherapy (3D-CRT) was performed with the equipment “linear accelerator Clinac 6EX” manufactured by “Varian Medical Systems Brasil Ltda[®]”, whose headquarters are in São Paulo that provides 6 MV photons beams. The planning of the radiotherapy was made with the System Eclipse Planning (version 7.1.35, Varian Medical System, Palo Alto, CA[®]) that calculates the distribution of the radiation inside the patient.

The protocol of radiation changes according to the area irradiated. In the breast, 45 to 50 Gy, divided in 25 fractions, with dose boost of 10 Gy in five fractions in the surgery bed. In case of irradiation of the thoracic wall, 45 to 50 Gy in 25 fractions, with *boost* of 10 Gy in 5 fractions in the scar (indicated for stage T3 or bigger and/or N+). When supraclavicular fossa is irradiated, 50 Gy in 25 fractions of the right anterior field (indicated in T4b or bigger, and/or N+).

The use of bolus is indicated for skin affected (T4b) or exiguous/positive margin in the thoracic wall. The indication of bigger boost dose depends if the skin was affected (T4b) or exiguous/positive margin in thoracic wall.

The data collected from the charts were tabulated and organized in the database elaborated with Microsoft[®] Excel

2013 and later processed in *software* Minitab 18® (Minitab Inc, State College, Pennsylvania). The variables were analyzed through univariate and multivariate statistic, with simple (*n*) and relative (%) frequencies. To verify the association between these variables, firstly, it was utilized the univariate analysis with Fisher exact test, t test, chi-square and statistic analysis of variance (Anova) for multivariate analysis. The level of significance assigned in the tests is 5% ($p < 0.05$), with confidence interval of 95% and sample error calculated of 8.4% (odds that the selection of the patients do not represent the population studied).

After the univariate analysis, the possible predictors by the higher level of significance ($p < 0.05$) were identified; next, the ordinal logistic regression was performed with the objective to represent the likelihood that an event occurs instead of another. The factors that demonstrate statistical significance and represented extremes of the study in question were selected: the development of extensive exudative radiodermatitis – score 3 (since score 4 was not observed) and mild dermatitis – score 1. In this analysis, the results of negative coefficient indicate more probability that the patient develops radiodermatitis score 3 instead of mild dermatitis.

RESULTS

In the analysis of the 117 patients, the mean age was 50 years \pm 21.60, only 1.7% were younger than 36 years, 6% older than 76 years, and the great majority of the patients had between 46 and 55 years (41%). The average size of the breasts obtained by the diameter between the entry in the field and exit of the field of radiotherapy was 23.1 cm \pm 2.97 and only one (0.85%) patient was male (Table 1).

Nearly 47% had comorbidities, the most common was hypertension, representing around 26% alone, the rest with background of diabetes, asthma, dyslipidemia, heart problems, glaucoma, intolerance to lactose, rhinitis and associations of these comorbidities. Overall, the patients were not tobacco addicted or alcoholic (63.25%), only 19.65% reported having had two habits conjointly in some phase of the life (Table 1).

The incidence of radiodermatitis was 81.19%, score 2 was the most prevalent (57.3%); score 4 was not observed in the study (Table 2).

About the stages of Classification TNM of breast cancer, it was verified score for metastasis (IV) in 11.97% of the patients. There was a slight predominance of stages IIA (23%) and IIIA (23.9%).

Previous treatments were found in 98.3% of the patients. The majority was submitted to surgery (91.45%) with the combined treatments: surgery and chemotherapy

Table 1. Frequency of the clinical and sociodemographic variables

Variables	Patients	%	Mean \pm SD
Age range			50\pm21.60
15 to 25	1	0.85	
26 to 35	1	0.85	
36 to 45	20	17.09	
46 to 55	48	41.03	
56 to 65	26	22.22	
66 to 75	14	11.97	
76 to 85	7	5.98	
Gender			
Female	116	99.15	
Male	1	0.85	
Size of the breast			23.1\pm2.97
From 12,5 cm to 16.5 cm	1	0.85	
From 16,6 cm to 20.5 cm	25	21.37	
From 20,6 cm to 24.5 cm	60	51.28	
From 24,6 cm to 30.5 cm	30	25.64	
Ore than 30.6 cm	1	0.85	
Mammary prosthetics			
Yes	9	7.69	
No	108	92.31	
Comorbidities			
Diabetes	5	4.27	
Diabetes and asthma	1	0.85	
Diabetes and dyslipidemia	1	0.85	
Diabetes and hypertension	10	8.54	
Hypertension	30	25.64	
Hypertension and asthma	1	0.85	
Hypertension and heart disease	1	0.85	
Hypertension and dyslipidemia	2	1.70	
Hypertension and glaucoma	1	0.85	
Hypertension, glaucoma and dyslipidemia	1	0.85	
Intolerance to lactose	1	0.85	
Rhinitis	1	0.85	
None	62	52.99	
Habits of life			
Tobacco addiction	10	8.55	
Alcoholic	10	8.55	
Alcoholic and tobacco addiction	23	19.65	
None	74	63.25	

Table 2. Relation of the degree of radiodermatitis presented by the patients post-radiotherapy 3D-CRT

Degree	Patients	%
0	22	18.8
1	7	6
2	67	57.3
3	21	17.9

(42.74%); and surgery, chemotherapy and hormone therapy (30.77%). Of the surgical modalities, 59.83% of the surgeries were radical and only 31.62%, conservative (nipples, skin sparing, quadrantectomies), only nine were reconstructed with mammary prosthetics.

In relation to the quantity of radiation applied, the average dose was 43.1 Gy \pm 6.55, the latter was fractioned in an average of 20 fractions \pm 5.97. The boost dose was

indicated for 72.6% of the patients, with average of 12.6 Gy \pm 2.5.

The clinical characteristics of the patients and the result of the multivariate analysis are shown in Table 3. In order to validate the association of multiple conditions for the development of radiodermatitis, it was performed the ordinal logistic regression where the risk of developing extensive exudative radiodermatitis score 3 (most severe type in this study) was evaluated in comparison with mild erythema – score 1. The result of the coefficient of the variable “dose of radiation” was - 0.175, with odd ratio OR = 0.84 (CI = 0.73-0.96%), and use of bolus was -1.121, OR = 0.33 (CI = 0.12-0.86), confirming there is a direct proportionality in the increase of the radiation dose and the severity of the injury as well as with the use of bolus and development of radiodermatitis score 3.

Table 3. Clinical characteristics of the patients and univariate statistical analysis

Variable analyzed	N=117		Presence of radiodermatitis		Valor-P*
	N°	%	Yes %	No %	
Existence of comorbidity	55	47	46	50	0.492 (QQ)
Habits of life					0.773(QQ)
Tobacco addiction	10	8.55	50	10	-
Alcoholic	10	8.55	90	10	-
Alcoholic and tobacco addiction	23	19.66	91.30	8.69	-
None	74	63.25	82.43	17.56	-
Classification of TNM staging TNM					<0.001(QQ)
Stage IA	11	9.4	81.81	18.18	-
Stage IIA	27	23.08	85.18	14.81	-
Stage IIB	18	15.38	83.33	16.66	-
Stage IIIA	28	23.93	78.57	21.42	<0.001(QQ)
Stage IIIB	13	11.11	92.30	7.69	<0.001(QQ)
Stage IIIC	6	5.13	83.33	16.66	-
Stage IV	14	11.97	64.28	35.71	-
Existence of previous treatment	115	98.3	81.73	18.26	0.034 (TF)
Conservative surgery	37	31.62	78.37	21.62	0.246(QQ)
Non-conservative surgery	70	59.83	82.85	17.14	0.020(QQ)
Received dose boost	85	72.6	88.23	11.76	0.001 (QQ)
Use of bolus (0.5 cm)					0.037(QQ)
Daily	19	16.24	89.47	10.52	0.009(QQ)
Every other day	15	12.82	86.66	15.38	-
Did not use	83	70.94	79.51	20.48	-
	Men	SD (\pm)			
Age range	50	21.60			0.244(TT)
Breast size	23.1	2.97			0.269(TT)
Dose (Gy)	43.32	6.55			0.011(Anova)
Dose boost (Gy)	12.6	2.50			0.001(QQ)
Quantity of fractions	20	5.97			0.050(TT)

Captions: SD: standard deviation; TT: test T; Anova: analysis of variance; QQ: chi-square; TF: exact test of Fisher; *The value – P < 0.05 is considered significant and is demonstrated in bold.

DISCUSSION

The aspects that related to the physical manifestation of radiodermatitis or increase of the toxicity level were: higher dose of radiation, increased fractionation of the dose, daily use of bolus, previous treatment, cancer staging, non-conservative surgery and application of boost dose. However, while using the ordinal logistic regression, only the variables “dose of radiation” and “use of bolus” matched the statistical model as predisposing factors of acute exudative radiodermatitis (score 3), showing major odd of developing more severe injuries after higher doses and use of bolus.

In the present study conducted with 117 patients, it is possible to indicate that 58% of the patients are in the age range between 36 and 55 years, being 99.15% females and one (n=1) male, confirming the low incidence of breast cancer in men as described by INCA¹. About the different scores of skin reaction, the results reveal low incidence of reaction score 3 (18.8%) in comparison to those with scores 1 and 2 (73.3%), data that are similar to the literature, which indicates 10-15% of the patients evolving to this score¹¹.

Whereas the patient-related factors, the size of the breast was not a predictive factor, but, differently from other studies that defined this measurement based in the size of the brassiere or with a ruler, in this analysis, the department of physical medicine of the health facility calculated the precise size of the breast through the program *External Beam Planning*, limiting its extension and grading in centimeters the spot of entry and exit of the field in the computed tomography conducted before the radiotherapy, showing that, possibly, these studies were biased^{6,12}.

The habits of life were also observed as predictors, probably because of the small number of individuals who claimed to be alcoholic or tobacco-addicted, a data that differs from several studies analyzed¹³⁻¹⁶.

Breast cancer staging had influence according to the statistical model. It was concluded that the patients in stages IIIA and IIIB are more prone to present score 3, probably because of the necessity of more aggressive treatment for further advanced stages. In the first stages of cancer, it must be emphasized, patients often present scores 1 or 2.

In relation to the factors connected with radiotherapy treatment, the hypofractionation of the doses was demonstrated by De Langhe et al.¹², as a factor to develop less dermatitis when compared to the patients that were submitted to standard fractionation. In a study of Ko et al (apud Bontempo)¹¹, it was verified that this method is being employed in

many treatment sites after the dose with a total of 4 mil Gy in 16 fractions, for the convenience of the patients and reduction of waiting line and costs. In the prospective study of the same authors with 133 breast cancer patients to evaluate the toxicity of the treatment with hypofractionation, it was verified that 14% did not develop radiodermatitis, 75% of the patients presented mild erythema and only 10%, moderate to vigorous erythema. The present study followed the same line of thought, demonstrating that hypofractionation is connected to lower scores and higher fractionation to elevated scores of dermatitis.

The dose of the radiation was shown to be a triggering factor not only of the physical manifestation, but of the increased severity of the skin reactions. Higher doses of radiotherapy are more damaging and the skin attempts to compensate while increasing the rate of baseline mitosis abnormally, causing skin thickening and dry desquamation. A still higher dose makes the baseline layer unable to recover itself and the exudate is released, which characterizes the moist desquamation⁸.

As opposed to Pignol et al.⁶, the boost dose was indicated as a factor related with the manifestation of radiodermatitis, because it increases even more the dose to be received by the patient. Likewise, the daily use of bolus instead of non-using or use every other day was demonstrated as a fairly predictive factor, a fact mentioned in other studies and of simple understanding, since it is a material utilized to increase the dose in the surface of the entrance of the field or to offset the lack of tissue^{15,16}.

The previous treatment with conservative surgery has shown itself as a protective factor for radiodermatitis, while the non-conservative (radical and simple) more associated to scores 2 or 3, a relation demonstrated in previous studies as of Tomo Suga et al (apud De Langhe)¹². This correlation may have not been noticed in the multivariate analysis because of the great number of radical surgeries conducted in this geographical region, reason for which the study presented a reduced number of conservative surgeries.

It is important to emphasize the presence of possible biases of the study such as the size of the sample and lack of calculation of the sample size (because it were collected data of all the patients eligible in the period) and its interference in the statistical calculations, the interview about habits of life, when many may have considered only the recent habits and omitted tobacco addiction or long time alcoholism, the large number of radical surgeries conducted in the region, sample of very heterogeneous patients, different types of radiotherapy (adjuvant and neoadjuvant) and the own model of retrospective study.

CONCLUSION

The main factors involved in the manifestation of radiodermatitis and who matched well to the two statistical models were the dose of the radiation and the use of bolus. In our case study, the size of the breast did not appear as a predictive factor of skin injuries in radiotherapy, however, our evaluation was more accurate than the observed in other studies, not based in subjective aspects. It is still possible to observe substantial variations of the frequency of cutaneous reactions in patients, but some of these aspects can be linked to added manifestation and intensification of these injuries, which permits the creation and application of prophylactic methods or protocols of prevention of radiotherapy services.

CONTRIBUTIONS

Cássia Cardoso Costa, Jorge Soares Lyra, Ricardo Akiyoshi Nakamura, Carine Medeiros de Sousa participated of the conception of the clinical trial and its planning, collection of data from medical charts, interpretation and statistical analysis, wording, critical review and approval of the final version of this article.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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