RTOG CRITERIA TO EVALUATE ACUTE SKIN REACTION AND ITS RISK FACTORS IN PATIENTS WITH BREAST CANCER SUBMITTED TO RADIOTHERAPY

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Purpose: Evaluate and classify skin reactions through the Radiation Therapy Oncology Group (RTOG) criteria and characterize factors that can intervene in these reactions. Method: Prospective study, with 86 women submitted to adjuvant breast radiotherapy with a total dose of 5040cGy, in a 6 MeV Linear Accelerator. Personal data were collected and breast size was measured (distance between field separation and breast height). The treated skin area was evaluated weekly. Results: Breast height and treatment technique were significant factors in the univariate analysis for the incidence of degree 3 skin reactions. However, only breast height was a significant factor in the multivariate analysis for the severity of skin reactions. The chances of occurring degree 3 reactions increase 2.61 times for each increase in height unit (cm). These findings allow nurses to plan more adequate and individualized procedures for each patient and contribute to the optimization of treatment.

DESCRIPTORS: radiotherapy; oncologic nursing; radiodermatitis; breast neoplasms

EVALUACIÓN DE LAS REACCIONES AGUDAS DE LA PIEL Y SUS FACTORES DE RIESGO EN PACIENTES CON CÁNCER DE MAMA SOMETIDOS A RADIOTERAPIA

El objetivo fue evaluar y clasificar las reacciones de la piel según los criterios del Radiation Therapy Oncology Group (RTOG) y caracterizar factores que puedan interferir en esas reacciones. Metodología: Estudio prospectivo, con 86 mujeres sometidas a la radioterapia en la mama, dosis total de 5040cGy, con Acelerador Lineal de 6 MeV. Fueron recolectados datos personales y medido el tamaño de la mama (distancia entre la separación de los campos y la altura de la mama). La evaluación de la piel del área de tratamiento fue realizada semanalmente. Resultados: La altura de la mama y la técnica de tratamiento fueron significativos en el análisis univariado, para incidencia de reacción de piel grado 3. Sin embargo, solamente la altura de la mama fue el factor significativo en el análisis multivariado para la gravedad de la reacción de la piel. La probabilidad de ocurrir una reacción grado 3 aumenta 2,61 veces por cada aumento de 1 unidad de altura en cm. Lo encontrado le permite al enfermero planificar conductas más adecuadas e individualizadas para cada paciente y contribuir para optimizar el tratamiento.

DESCRIPTORES: radioterapia; enfermería oncológica; radiodermatitis; neoplasias de la mama

AVALIAÇÃO DAS REAÇÕES AGUDAS DA PELE E SEUS FATORES DE RISCO EM PACIENTES COM CÂNCER DE MAMA SUBMETIDAS À RADIOTERAPIA

O objetivo deste estudo foi avaliar e classificar as reações de pele, segundo os critérios do Radiation Therapy Oncology Group (RTOG) e caracterizar fatores que possam interferir nessas reações. A metodologia usada foi o estudo prospectivo, com 86 mulheres submetidas à radioterapia na mama, dose total de 5040cGy, com Acelerador Linear de 6 MeV. Coletou-se dados pessoais e foi medido o tamanho da mama (distância entre a separação dos campos e altura da mama). A avaliação da pele na área de tratamento foi realizada semanalmente. Concluiu-se que a altura da mama e a técnica de tratamento foram significantes na análise univariada, para incidência de reação de pele grau 3. Porém, apenas a altura da mama foi fator significante na análise multivariada para a gravidade da reação de pele. A chance de ocorrer reação grau 3 aumenta 2,61 vezes a cada aumento de 1 unidade de altura em cm. Esses achados permitem ao enfermeiro programar condutas mais adequadas e individualizadas a cada paciente e contribuir para a otimização do tratamento.

DESCRITORES: radioterapia; enfermagem oncológica; radiodermatite; neoplasias da mama

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INTRODUCTION

Radiotherapy has been used as adjuvant therapy in patients with breast cancer submitted to conservative surgeries in initial stages. It aims to diminish loco-regional recurrence and favor survival[1-2].

Skin reaction is one of the frequent adverse reactions that occur in patients submitted to breast cancer radiotherapy. Acute radiodermatitis begins around the second/third week of treatment, due to destruction of cells in the epidermal basal layer (loss of permeability) with exposure of the dermis (inflammatory process), and is manifested as erythema, which can either progress to exudative dermatitis or not[3-4].

In 1982, the Radiation Therapy Oncology Group (RTOG) developed the Radiation Morbidity Scoring Criteria to classify radiotherapy effects. It identifies degree 0 (no reaction), 1 (faint erythema, dry desquamation, epilation, diminished sweating), 2 (moderate, brisk erythema, exudative dermatitis in plaques and moderate edema), 3 (exudative dermatitis, besides cutaneous folds and intense edema) and 4 (ulceration, hemorrhage, necrosis). RTOG score has been widely employed for more than 25 years and is accepted and acknowledged by medical and nursing communities[5].

The severity of skin reactions is attributed to factors related to radiation, such as total dosage, fractioning scheme, radiation energy (type of equipment), volume of irradiated tissue and radio-sensitivity of the tissue involved. It is believed that patient-related factors, such as age, smoking, coexistent chronic diseases and concomitant antineoplastic treatment can interfere in skin reactions due to the altered healing process[3].

It has been observed that breast size is an important factor for stronger skin reactions. Large breasts receive larger irradiation doses on the skin to assure adequate dosage in deeper structures and tissues[6]. Thus, a significant part of the skin and breast fold is exposed to radiation, increasing the irradiated volume[6]. However, there is no mathematical parameter in literature that indicates how much breast size increases chances of more severe acute skin reactions.

Accurate knowledge on factors inherent to patients, related to the disease and to the treatment and their importance for the severity of skin reactions, can certainly contribute to orientation and individualized care, implementation of nursing care and optimization of treatment. Recording this information contributes to evaluate the patient at any moment, to follow-up the treatment in a more complex way and offer quality care[7].

Therefore, this study aimed to evaluate and classify skin reactions according to the RTOG criteria and characterize potential factors related to the treatment and those inherent to patients that can interfere in the reactions of women with breast cancer submitted to radiotherapy.

Because of the above, observation and classification of skin reactions caused by radiotherapy, verification of factors related to the treatment or intrinsic to each patient, which can aggravate reactions, are relevant for orientations to these patients, so that they can take adequate measures to minimize and/or treat them, optimizing the treatment.

CASUISTIC AND METHOD

This prospective study involved 86 women with breast cancer diagnosis, who were submitted to surgery (stages I, IIa and IIb) and adjuvant radiotherapy in the Radiotherapy Centers at the Federal University of São Paulo (UNIFESP) and the Hospital Alemão Oswaldo Cruz (HAOC). The Research Ethics Committees from both institutions approved the study and all patients signed the free and informed consent term. Data were collected according to the evaluation instrument, with questions on histological type, age, coexistent diseases (diabetes, hypertension), previous or concomitant antineoplastic treatment (scheme and date), smoking and family cancer history. Women older than 18 year, who were submitted to quadrantectomy or mastectomy with reconstruction, were included in the study. Radiotherapy was performed on the breast region, tangential and parallel opposed fields, with a total dose of 5040cGy (180cGy dose/day), with 6 MeV linear accelerator. Two treatment techniques were used: Source to skin distance (SSD) and isocenter. The breast size was obtained from the contour drawing. The distance between the field separation and the breast height was measured (Figure 1).

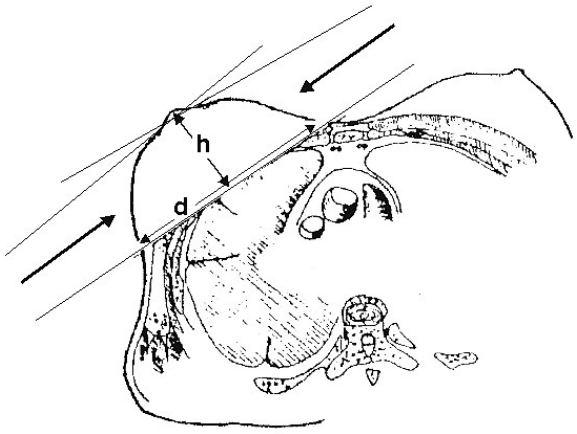

Figure 1 – Breast distance measure (d) and height (h)[8]

All topical products prescribed by the physicians were also recorded, though, due to their variety, they were only considered as adjunct factors in the irradiation effect on the skin.

Two observers (physician and researcher) evaluated the treated skin area every week during the six weeks of treatment and reactions were classified using the RTOG scale. Breasts were marked in the following regions: superior exterior quadrant (QSE), superior internal quadrant (QSI), inferior external quadrant (QIE), inferior internal quadrant (QII), central quadrant (QC) and inframammary region (IM). Reaction in the IM region was considered only when lesion was located specifically in this region, which differentiates from alteration in the inferior quadrants.

Degrees 1 and 2 were grouped for statistical analysis because they cause mild symptoms and require simple conducts, which do not limit the continuity of treatment. Fisher's test was used to analyze categorical variables and the numerical variable age in relation to skin reactions. To evaluate numerical variables, breast distance and height, in relation to skin reactions, box-plots, Fisher's test and Logistic Regression were used. To jointly evaluate the parameter technique and breast height in relation to skin reactions, box-plots and Logistical Regression were used. All tests were fixed at a 5% significance level.

RESULTS

Table 1 shows the quantity of patients with degree 1, 2 and 3 skin reactions.

Table 1 – Incidence of different degrees of skin reactions due to radiotherapy. São Paulo, 2007

Reactions	N	%
Degrees 1 and 2	71	82.6%
Degree 3	15	17.4%
Total	86	100%

Table 2 shows the statistical results of logistic regression in relation to breast height.

Table 2 – Final model of logistic regression according to breast height. São Paulo, 2007

Model	Coefficient	Coefficient standard-error	Descriptive level (p)	Coefficient exponential
Height	0.9586	0.2702	<0.001	2.61
Constant	-8.5891	2.1120	<0.001	0.00

Chances of occurring degree 3 reactions (RTOG) increase 2.61 at each increased height unit (cm).

The parameter breast height showed statistical significance for the occurrence of degree 3 reactions according to Figure 2.

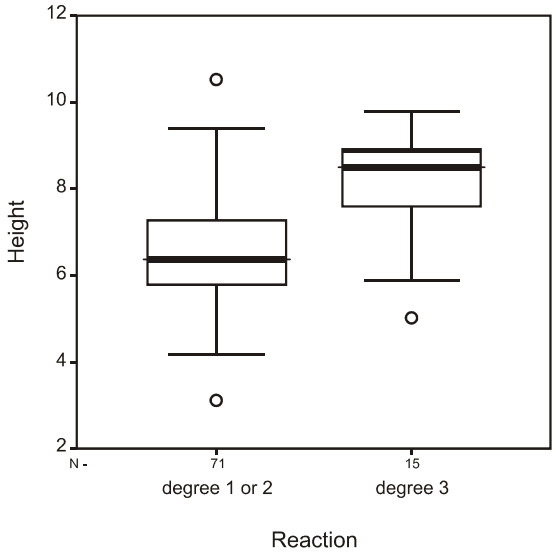

Figure 2 – Breast height according to the type of skin reaction (d1/d2 e d3). São Paulo, 2007

Figure 3 shows the multivariate analysis to verify the relevance of treatment technique and breast height for skin reactions.

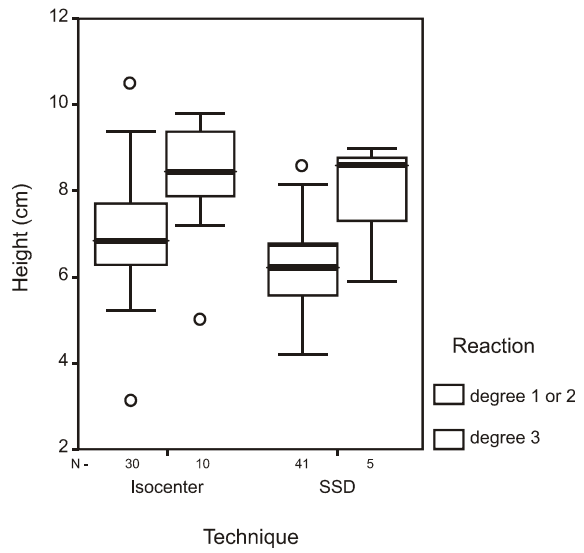

Figure 3 – Height and treatment technique in relation to the type of skin reaction. São Paulo, 2007

DISCUSSION

Breast skin reaction during radiotherapy, though reversible in the majority of cases and less frequent than in the past, is the most common side effect in these patients and can affect the therapeutic program and worsen quality of life. It occurs in several phases of the treatment, initiates with mild intensity and can develop to an intense degree, hindering the continuity of applications. This variety of intensities depends on factors related to radiation and individuals. Thus, in this study, these parameters were characterized in the study population and skin reactions were correlated.

Antecedent cancer history is an expected factor. Sixty-five percent of cancer incidence is observed in our patients' families, while an incidence of up to 82.5%[3] is found in literature. It was not possible to show significance, probably due to the sample number.

Regarding the different levels of skin reactions, the results reveal low incidence of degree 3 reactions (17.4%) in comparison to degrees 1 and 2 (82,6%) (Table 1). These data are comparable to those found in literature, in which studies show evolution to degree 3 from 10 to 15% and from 7 to 20%[9]. When the breast region and the degree of skin reaction are evaluated, 100% of degree 3 reactions were in the inframammary region. Such results are found in several studies, which show the predominance of degree 3 reactions in this region because of the constant friction and higher humidity in this area[3,10].

With regard to smoking, this factor did not show statistical significance, probably due to the low incidence of smokers in this population. The results showed only 11.6% of smokers (10 patients), while only one patient presented degree 3 reactions. There is controversy in the literature regarding this issue and, according to some authors, smoking does not increase the risks for skin reactions[1]. Anoxia chronically caused by the smaller index of oxyhemoglobin could even diminish the chances of causing skin reaction because oxygen functions as a radiosensitizer and its absence on skin would provide resistance to the reaction[1]. However, considering radiobiological aspects, oxygen does not sensitize tissues with physiological levels of oxygen but those with low levels. Nevertheless, the reaction could be worsened because of the nicotine and carbon monoxide[11] action, which can hamper the healing process. Thus, further research is needed on the mechanisms of lesion caused by the association of radiation and smoking and its importance as a risk factor for skin reactions and healing process.

Regarding diabetes, only 8.1% of patients in this study presented the disease. The small sample size possibly did not permit statistical significance for this parameter. However, no other study has showed diabetes as a predisposing factor for the incidence of more intense skin reactions. Because it is a systemic pathology that interferes in healing phases, however, it can delay healing and expose patients to higher risks of infection[6].

In terms of hypertension, only 24.4% of patients in this study were hypertensive and no statistical significance was obtained with relation to the severity of skin reaction. Hypertension is not considered a predictive factor of skin reactions, though it is a disease frequently associated to other co-morbidities.

The average age of patients who had degree 3 reactions was higher. Differences were observed between the average age of patients with degree 1 or 2 (58.31) and degree 3 reactions (64.47), but they permitted borderline significance, probably due to the size of the sample ($p = 0.062$), though it suggests a tendency of degree 3 reactions in older women. Literature shows that radiotherapy is well tolerated in old patients and it is not the only contraindication for the treatment[3]. Yet, some authors suggest that, because old people present smaller mitosis indices, they would be less sensitive to radiation, which destroy cells mainly in the mitosis phase and, consequently,

would cause weaker skin reactions[3]. However, the elderly also present diminished production of collagen and fibroblasts which, when associated to co-morbidities (most frequent in older women), can harm the healing process[3].

The researchers have observed in their daily practice that age per se is no reason for concern. Nevertheless, when age is associated to co-morbidities, patients deserve a care program focused not only on skin reactions, but also on encouragement to self care and maintenance of health in other levels, like the emotional and physical, among others.

Regarding treatment characteristics, it was observed in this study that previous or concomitant chemotherapy with radiotherapy was not a significant factor for the severity of skin reactions, probably also because of the small number of patients in these situations. Different protocols and drugs were used for the treatment. Literature does not show significant interference of pre-radiotherapy chemotherapy in skin reaction, but explains that young patients have a high cellular turn-over, which increases susceptibility to adverse reactions in the site[12]. However, studies have shown that chemotherapy concomitant with radiotherapy significantly increases skin reactions in these patients. Studies have also shown that antracyclic drugs cause more adverse reactions than the association of Cyclophosphamide, Methotrexate and 5-Fluorouracil (CMF), though both can interfere in the intensity and severity of skin reactions[2].

No statistically significant difference was found in this study regarding the use of concomitant hormonotherapy. Again, this result might be due to the small number of patients with this characteristic. The influence of tamoxifen on the incidence of pulmonary fibrosis has been showed, but its effect on skin has not been reported[10].

Reconstructive surgeries were performed in 11 patients (12.7%). The small sample size did not permit verifying statistical significance in this case either, but no patients developed degree 3 reactions in this study. There is controversy in the literature regarding radiotherapy after breast reconstruction surgery, though the great concern is related to the late effects of radiotherapy and not to skin reactions during or right after the treatment[13]. In relation to data obtained in this study, possibly because reconstructed breasts are smaller and not flab, they do not favor humidity, friction and higher dosage distributed on the skin, which would prevent inframammary reactions.

Regarding topical therapy, 65.1% (N=56) of patients used creams prescribed by radiotherapists and there was a great variety of products. There is controversy on their goal, regarding the prevention of skin reactions, relief of symptoms or treatment with the several products studied[3-4,6,11-14]. Corticosteroids and non-steroidal anti-inflammatory drugs are frequently used for moderate to intense reactions. However, they do not diminish inflammatory response, delay all phases of the healing process and increase the risk of local infection. Thus, they are indicated for a limited time period[3].

Several studies consider breast size of great importance because the volume irradiated is a factor related to radiation and interferes in the incidence and severity of side effects. There are several models of breast measure to relate with skin reaction. The bra size, maximum breast diameter[10] and volume in centimeters^3 were considered[14]. The breast curve drawing obtained in the planning for dosage calculation was used in this study as previously reported. This measure is considered reliable and easy to obtain and reproduce. The measures were statistically analyzed regarding their influence on skin reaction.

Breast distance was not a statistically significant factor in the data analysis. The researchers believe that this result occurred because breast distance does not necessarily represent larger breasts. In relation to the breast height, this parameter showed statistical significance for the occurrence of degree 3 reactions (Figure 2). Patients with degree 3 reactions presented a higher average breast height than patients with degree 1 and 2 reactions (8.15 cm and 6.53cm respectively). Larger breast volumes require that larger doses be applied on skin to reach the desired dosage in tissue and deeper structures. In addition, adipose tissue has little vascularization and can delay any healing process[6]. These results corroborate with those found in literature that show a proportionally more intense skin reaction in medium and large breasts[15]. Data in the present study also show that the chance of degree 3 reactions increases 2.61 times at each height unit (cm) (Table 2).

Regarding the treatment technique used, statistical difference was found in univariate analysis between the isocenter and SSD techniques, showing that the isocenter technique would increase the chance of degree 3 skin reactions. Nevertheless, no study was found comparing these two techniques or showing higher incidence of skin reaction when the isocenter technique is used.

Therefore, multivariate analysis had to be used to verify the importance of the treatment technique and breast height for skin reactions. This result definitely showed that the technique is not a significant parameter for the occurrence of degree 3 skin reactions, when breast height is considered (Figure 3).

When the results were jointly analyzed, they revealed low incidence of degree 3 skin reactions in the study population, and also that, when they occurred, the inframammary region was the most frequently affected area. They also show that breast volume is the most important factor for the severity of skin reactions in patients submitted to radiotherapy in the breast region. Despite the low incidence of severe skin reaction, care with the irradiated skin is a relevant factor for radiotherapy in breast cancer. There is little consensus between involved professionals, and knowledge advancements regarding the care of wounds have little impact on patients with skin reactions caused by radiation[16-18]. In this context, the nurse is an important professional in care for these patients. Such care has to be based on each patient's- individual data, breast physical exam, and data collection on planning, with special attention to breast height. These procedures allow for better evaluation of the probability of undesirable effects of radiotherapy and, then, adequate planning and individualized care with a view to an uninterrupted treatment and, consequently, better clinical response. These measures allow for optimization of radiotherapy and nursing care delivered to these patients.

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