Effect of radiotherapy on pulmonary function and fatigue of women undergoing treatment for breast cancer

Efeito da radioterapia na função pulmonar e na fadiga de mulheres em tratamento para o câncer de mama

Efecto de la radioterapia en la función pulmonar y en la fatiga de mujeres en tratamiento para el cáncer de mama

Dayane Evellyn dos Santos[1], Mariana Tirolli Rett[2], Andreza Carvalho Rabelo Mendonça[3], Thaysa Samanta Bezerra[1], Josimari Melo DeSantana[2], Walderi Monteiro da Silva Júnior[2]

ABSTRACT | This study compared the pulmonary function and fatigue in patients before and after adjuvant radiotherapy (RT) and correlated the pulmonary function with the radiotherapy dose and fatigue. A longitudinal and observational study was conducted involving 20 women. Pulmonary function was evaluated by digital lung spirometry (ClementClarke®) and manometry (GlobalMed®, model MVD 300) and fatigue was analyses by the Functional Assessment of Cancer Therapy Fatigue (FACT-F). All evaluations were conducted before the first RT session and up to one week after this treatment. Statistical analyses were conducted by the Wilcoxon Signed Rank Test and Spearman, considering $p<0.05$. There was significant reduction at spirometry parameters: forced vital capacity (23.52%), forced expiratory volume in the first second (26.23%), peak expiratory flow (10.12%) ($p=0.001$). Maximal expiratory pressure (25.45%) and maximal inspiratory pressure (32.92%) also showed significant reduction at manometry. There was a significant reduction on physical well-being and functional well-being and a significant increase in fatigue evaluated by the FACT-F ($p=0.001$). There was no correlation between pulmonary function, radiation dose and fatigue. Short-term effects of radiotherapy showed reduction of pulmonary function, but the values were considered similar to normal. There was a significant increase in fatigue, and significant decrease of physical well-being and functional well-being.

Keywords | breast neoplasms; radiotherapy; respiratory function tests; radiation effects; fatigue; physical therapy.

RESUMO | O presente estudo comparou a função pulmonar e a fadiga de mulheres antes e após a radioterapia (RT) adjuvante para tratamento do câncer de mama, e correlacionou a função pulmonar com a dose de radiação e fadiga. Foi conduzido um estudo observacional longitudinal envolvendo 20 mulheres. A função pulmonar foi avaliada pela espirometria (ClementClarke®) e manovacuometria (GlobalMed®, modelo MVD 300), e a fadiga pelo Functional Assessment of Cancer Therapy Fatigue (FACT-F). Todas as avaliações foram realizadas antes da primeira sessão e uma semana após o término da RT adjuvante. Para a análise estatística foram utilizados os testes Wilcoxon Signed Rank Test e correlação de Spearman, adotando-se nível de significância $p<0,05$. Na espirometria, encontrou-se redução significativa da capacidade vital forçada (23,52%), do volume expiratório forçado no primeiro segundo (26,23%) e do pico de fluxo expiratório (10,12%) ($p=0,001$). As pressões expiratórias e inspiratórias máximas também diminuíram significativamente (25,45 e 32,92%, respectivamente). Observou-se diminuição significativa do bem-estar físico e do bem-estar funcional, e um

Study carried out at Fundação de Beneficência Hospital Cirurgia (FHBC) and in Hospital de Urgências de Sergipe (HUSE) – Aracaju (SP), Brazil.
[1]Physical Therapist by Universidade Federal de Sergipe (UFS) – Aracaju (SE), Brazil.
[2]Physical Therapist; Adjunct Professor at UFS – Aracaju (SE), Brazil.
[3]Physical Therapist; Master's degree student at the Postgraduate Program in Health Sciences at UFS – Aracaju (SE), Brazil.

Correspondence to: Mariana Tirolli Rett – Rua Claudio Batista, s/n – Santo Antonio – CEP: 49060-100 – Aracaju (SE), Brazil – E-mail: mariana@ufs.br
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aumento significativo da fadiga no FACT-F (p=0,001). Não foram observadas correlações entre as variáveis da função pulmonar com a dose de radiação e fadiga. Em curto prazo, a RT promoveu redução na função pulmonar, mas a mesma permaneceu próxima à normalidade para a amostra estudada. Observou-se aumento significativo da fadiga e diminuição dos escores dos domínios bem-estar físico e funcional.

Descritores | neoplasias da mama; radioterapia; testes de função respiratória; efeitos de radiação; fadiga; fisioterapia.

RESUMEN | El presente estudio comparó la función pulmonar y la fatiga de mujeres antes y después de la radioterapia (RT) como ayudante para el tratamiento del cáncer de mama, y se correlacionó la función pulmonar con la dosis de radiación y fatiga. Fue realizado un estudio observacional longitudinal involucrando 20 mujeres. La función pulmonar fue evaluada por espirometría (ClementClarke®) y manovacuometría (GlobalMed®, modelo MVD 300) y, la fatiga fue evaluada por la Functional Assessment of Cancer Therapy Fatigue (FACT-F). Todas las evaluaciones fueron realizadas antes de la primera sesión y una semana después del término de la RT. Para el análisis estadístico fueron utilizados los tests Wilcoxon Signed Rank Test y correlación de Spearman, adoptando un nivel de significancia p<0,05. En la espirometría, se encontró reducción significativa de la capacidad vital forzada (23,52%), del volumen espiratorio forzado en el primer segundo (26,23%) y del peak de flujo espiratorio (10,12%) (p=0,001). Las presiones espiratorias e inspiratorias máximas también disminuyeron significativamente (25,45% y 32,92%, respectivamente). Se observó disminución significativa del bienestar físico y del bienestar funcional, y un aumento significativo de la fatiga en el FACT-F (p=0,001). No fueron observadas correlaciones entre las variables de la función pulmonar con la dosis de radiación y fatiga. En corto plazo, la RT promueve la reducción de la función pulmonar, pero los valores son considerados similares a los normales. Se observó aumento significativo de la fatiga y disminución de los puntajes en los dominios de bienestar físico y funcional.

Palabras clave | neoplasias de la mama; radioterapia; test de función pulmonar; efectos de radiación; fatiga; fisioterapia (especialidad).

INTRODUCTION

Breast cancer is the main cause of death due to malignant diseases among Brazilian women, and 52,680 new cases were expected for 2012[1]. Despite the evolution in diagnosis and treatment, the surgical procedures and complementary therapies, such as radiotherapy, chemotherapy and hormone therapy are still prevalent[2-4].

Radiotherapy (RT) is capable of destroying tumor cells, reducing the risk of local recurrence and increasing survival rates[5,6]. The most common application technique is the external RT (teletherapy), in which ionizing radiation goes through different tissues before reaching the tumor area; therefore, organs and normal tissues are subjected to the toxic effects of the emitted rays[7]. The absorption of radiation can cause biochemical changes and cell damage both immediately and later on[8-10].

After RT, some side effects are likely to occur, such as: pain, skin changes, mobility restriction, local sensitive change and fatigue[8,9]. Pulmonary changes with radiological abnormalities, such as the increased density, symptomatic radioactive pneumonitis, pulmonary fibrosis, ventilation deficit and quantitative reduction in pulmonary function tests can also be expected[7,10-14].

Added to the mentioned changes, fatigue after RF can compromise the execution of daily activities, social and family contact, besides causing work loss[15]. This symptom has a multifactorial causes and can be related to the RT itself, as well as physical and psychological factors[16,17].

In national literature, the evaluation of fatigue concomitant with the assessment of pulmonary function during treatment with RT for breast cancer was not found. Thus, knowing the potential effects of RT can enable the prevention and treatment of such disorders. Therefore, the objective of this study was to compare the pulmonary function and fatigue of women submitted to surgery for breast cancer before and after adjuvant RT. It also aimed at correlating pulmonary function with the radiation dose and fatigue.

METHODOLOGY

An observational and longitudinal study was performed from August to October 2011. Women submitted to mastectomy and quadrantectomy, with axillary lymphadenectomy and prescription for adjuvant RT were included. The excluded patients were those submitted to bilateral surgery, breast reconstruction or placement of breast prosthesis, with history of pneumopathy (lung cancer, pulmonary emphysema, chronic obstructive pulmonary disease, bronchiectasis), concomitant chemotherapy and neoadjuvant RT. Twenty-five women were eligible for the study, however 5 were excluded for interrupting radiotherapy, so 20 women remained.

RT was performed from five to six weeks (depending on the dose) with daily applications. The irradiated

regions were: breast region (or plastron), and the axillary region and clavicular fossa with lower doses.

Pulmonary function was assessed by the spirometry (ClementClark®) and manovacuometry tests (GlobalMed®, MVD 300 model), which measure capacities and volumes, and respiratory muscle strength, respectively.

Spirometry was conducted according to the criteria by the American Thoracic Society[18]. The forced vital capacity (FVC) was assessed in liters (L), the forced expiratory volume (FEV1), in L, the FEV1/FVC ratio, in %, and the peak expiratory flow (PEF), in liters per minute (L/min). For this test, patients were told to perform maximal inspiration, until the full lung capacity (FLC), followed by a continuous and forced expiration, until the residual volume (RV), in the mouthpiece of the device. The obtainment of three acceptable (with variation of PEF values lower than 10%) and reproducible curves (with the two highest values of FEV1 and FVC, with variation lower than 0.15 L) were considered, adopting the highest values measured from each variable.

Manovacuometry followed the procedure proposed by Neder et al.[19]. A deep and prolonged inspiration was required, until FLC, followed by forced expiration on the mouthpiece of the device to obtain the maximal expiratory pressure (EPmax). For the maximal inspiratory pressure (IPmax), a forced expiration was requested, until RV, followed by deep inspiration. Three EPmax and IPmax maneuvers were performed with a one minute interval. The highest obtained value was registered, considering the performance of three acceptable and reproducible maneuvers, with the maximum of 10% of difference between them.

To assess fatigue, the Functional Assessment of Cancer Therapy Fatigue (FACT-F) was used, which consists of 40 items, being 27 related to the Functional Assessment of Cancer Therapy-General (FACT-G) and 13 specific items about fatigue[20]. The questions in FACT-G are distributed into domains about physical well-being, social/family well-being and functional well-being (each with 7 items and a 0 to 28 score) and emotional well-being (7 items and a 0 to 24 score). In these domains, the higher the score, the better the assessed well-being. The fatigue subscale has a 0 to 52 score, and the higher the score, the lower the fatigue. There is a total score corresponding to the sum of domains and the fatigue subscale, ranging from 0 to 160, and the higher the score, the lower the fatigue.

All evaluations were performed by the same evaluator in two moments: before the first RT session and a week after its conclusion. The study was approved by the Research Ethics Committee of *Universidade Federal de Sergipe* (UFS) – CAAE 0090.0.107.000-11. The statistical analysis was conducted by BioEstat 5.0 and the Wilcoxon Signed Rank test and Spearman's correlation test were used, with a $p<0.05$ significance level.

Table 1. General, clinical and surgical characteristics (n=20)

Age (years)	53.5±11.22
BMI (kg/m²)	26.47±3.41
Surgical treatment	
Radical mastectomy	10 (50%)
Quadrantectomy	10 (50%)
Laterality	
Left side	6 (30)
Right side	14 (70)
Time between surgery and RT (months)	5.9±2.8
Radiotherapy	
Daily dose (cGy)	186.75±23.22
Total dose (cGy)	5.054±805.92
Duration (days)	27±2.21

BMI: body mass index; kg/m²: kilogram/meter²; RT: radiotherapy; cGy: centigrays.

RESULTS

The general, clinical and surgical characteristics of the 20 women are described in Table 1. Only one had worked in an environment with dust, two were smokers and three had smoked for about four years.

Spirometry showed a significant decrease in FVC (23.52%), FEV1 (26.23%) and PEF (10.12%), (p=0.001). The FEV1/FLC ratio did not present significant changes (p=0.430) (Table 2).

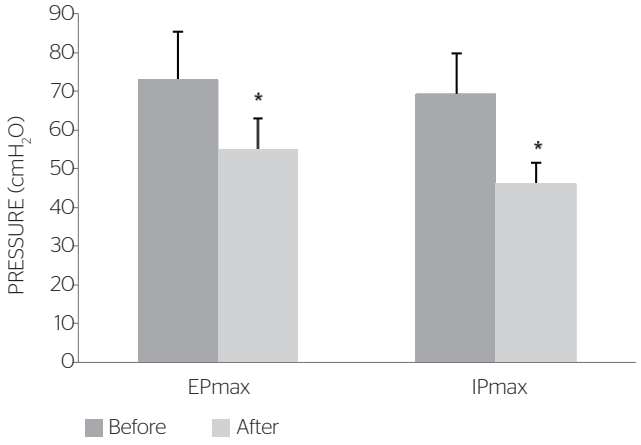
Table 2. Comparison of spirometry before and after radiotherapy (n=20)

Spirometry	Before	After	% reduction	p value
FVC (L)	2.56±0.38	1.95±0.37	23.52±5.98	0.001*
FEV1 (L)	2.04±0.37	1.50±0.31	26.23±10.15	0.001*
PEF (L/min)	315.05±26.45	282.25±20.34	10.12±6.32	0.001*
FEV1/FVC (%)	76.05±3.73	72.20±3.73	0.7±7.53	0.43

%reduction: 100*(final - initial)/initial; FVC: forced vital capacity; FEV1: forced expiratory volume; PEF: peak expiratory flow; L: liter; L/min: liter/minute; *p<0.05, comparison before and after radiotherapy

Significant reduction in respiratory muscle strength was found: EPmax was initially 73±12.47, and after RT, 55±7.90 cmH_2O, which is similar to a 25.45% reduction. IPmax went from 69.50±10.41 to 46.25±5.32 cmH_2O, corresponding to a 32.92% reduction (p=0.001) (Figure 1).

The significant aggravation of the physical well-being was observed, decreasing from 22.45±5 to 16.75±5.5, as well as of the functional well-being, from 17.35±5.5 to 14.95±5.2 and the fatigue subscale, from 46.1±4.9 to 26.1±6.8 (p=0.001) (Figure 2).



EPmax: maximal expiratory pressure; IPmax: maximal inspiratory pressure
*p<0.05, comparison before and after radiotherapy

Figure 1. Comparison of manuvacometry (EPmax and IPmax) before and after radiotherapy.

*p<0.05, comparison before and after radiotherapy.

Figure 2. Scores of the Functional Assessment of Cancer Therapy Fatigue domains and of the fatigue subscale before and after radiotherapy

The total FACT-F score also presented significant reduction, from 114.70±12.60 to 85.10±14.00 (p=0.001). No significant correlation was found between the pulmonary function after RT and the total radiation dose, with the fatigue subscale and with the total FACT-F score (Table 3).

DISCUSSION

A reduction in the main pulmonary function measures was observed (FVC, FEV1, EPmax and IPmax), as well as the aggravation of the physical and functional well-being and fatigue. Despite the decreased pulmonary function and the reduction of more than 20% of FVC and FEV1, the values remained within normality, according to weight, age and height of the studied sample[18,19]. Changes in lung capacity and volume are expected after RT[11,21-25], since there are potential risks of damaging the pulmonary parenchyma, losing type ii pneumocytes, losing surfactant and edema in the basement membrane[26]. But there is also the possibility that the patient can remain asymptomatic or never present any changes, be it in the parenchyma or in the pulmonary function, due to the "compensation in relation to the health lung", which did not receive radiation[24].

In the short term, the effects of RT did not cause an impact on the pulmonary function, even with the decrease of some spirometry and manovacuometry parameters, maybe because of the radiation dose, or the short follow-up time, or even because of the "compensation of the health lung". In the study by Schettino, Jotta e Cassali[25], the authors used the same instruments to assess pulmonary function, but they did not find any changes immediately after RT. However, this study involved only ten women.

More damage in the pulmonary function and in the capacity of alveolar diffusion is demonstrated by studies

Table 3. Correlation of pulmonary function values (spirometry and manovacuometry) after radiotherapy with the total radiotherapy dose, the fatigue subscale score and the total score of the Functional Assessment of Cancer Therapy Fatigue (n=20)

Pulmonary function	Total RT dose		Fatigue subscale score		Total FACT-F score	
	r	p value	r	p value	r	p value
FVC	-0.36	0.11	-0.07	0.75	0.32	0.12
FEV1	0.20	0.37	-0.14	0.54	-0.03	0.86
PEF	-0.28	0.21	-0.09	0.70	0.02	0.29
FEV1/FVC	-0.29	0.90	-0.16	0.49	0.18	0.42
EPmax	-0.41	0.17	-0.32	0.15	0.41	0.15
IPmax	-0.32	0.16	-0.22	0.34	0.38	0.11

RT: radiotherapy; FACT-F: Functional Assessment of Cancer Therapy Fatigue; FVC: forced vital capacity; FEV1: forced expiratory volume; PEF: peak expiratory flow; EPmax: maximal expiratory pressure; IPmax: maximal inspiratory pressure; r: Spearman's correlation

with longer follow-up and higher number of reassessments after RT[4,5,23-25]. Ooi et al.[24], in a prospective study performed 1, 3, 6 and 12 months after the conclusion of RT, showed that RT can be associated with an irreversible reduction of FCV, FEV1 and the carbon monoxide diffusing capacity.

The deficit in ventilation and in the capacity of alveolar diffusion that occurs in the irradiated lung can be related to the used technique, to the total dose, to the fractionated dose and the volume of the lung which received radiation[8,12,13]. Lung disorders can be temporarily classified as actinic pneumonitis, which appears from three to six months, and pulmonary fibrosis, which occurs about one year after RT[26]. Due to the period in which they were reassessed, until one week after the conclusion of RT, the patients did not present with any characteristic symptom of the aforementioned chronic lesions. Besides, no significant correlation between pulmonary function and total radiation dose was found, which is in accordance with the profile of the studied patient[23].

Imaging tests can also be useful[5,6,12], because at an acute phase, radiation can lead to the appearance of attenuation or consolidation areas in lung x-rays, while at a late stage, bronchiectasis areas and loss of volume can be observed[10,12]. However, it was not possible to demonstrate radiological changes in this study, because only tests of pulmonary function and fatigue assessment were conducted.

It is worth to mention that even without clinical repercussion, the decrease of EPmax and IPmax was observed. EPmax is connected with the promotion of an effective coughing and elimination of secretions[25], so, its aggravation can compromise the clinical picture of these patients if, in the long term, they present with some pulmonary disorder. Such reduction in the respiratory muscle strength can be associated with changes that take place in the pulmonary parenchyma, besides tiredness and physical exhaustion reported by the patients after RT.

Besides pulmonary repercussions, RT can cause fatigue. This has been shown by the decrease of the fatigue subscale, the FACT-F general score and the aggravation of the physical and functional well-being. These domains had complaints of indisposition, lack of energy, somnolence, loss in the work activities, pain, among others. According to literature and the clinical practice, the presence of fatigue, tiredness and physical exhaustion as a secondary effect of RT[8] has a negative repercussion on the performance of daily life tasks, socialization, recreational activities and in the global physical conditioning[15,26].

Even though there have been correlations between pulmonary function and fatigue, the reduction of values such as volume, capacities and respiratory muscle strength can also influence the appearance of fatigue[26]. The symptoms of lack of energy, tiredness, and intolerance to effort can be a reflex of the RT itself, of psychological factors, of the need to sleep/rest during the day[8,15,21,26], and they can even be increased by the negative repercussions of RT on the respiratory function[26]. Clinically, it is expected that when the pulmonary function is compromised, even if temporarily or without great repercussions, the patients can experiment situations of indisposition or exhaustion.

The scores of the family and emotional well-being domains are in accordance with those of literature, when considering women who are being treated for breast cancer[20] and did not present differences after RT. It is believed that these women have proper family support and receive support from their friends, at home and in their social environment, which justifies the lack of compromise in this aspect. Besides, they may work with strategies to face the disease, which does not compromise the emotional well-being.

Even though the values of capacities, volumes and respiratory muscle strength are within normality for the studied sample, and considering the spirometry as an important indicator of risk for the development of pulmonary diseases[18], the reduction of the assessed parameters confirms the potentially negative effect caused by RT, in the short term, on the pulmonary functional reserve[6]. It is clear that these results should be considered important, since the life expectancy of women with breast cancer has increased, they have been adopting a more active life style, and due to the fact that this sample represents different women who, in the same age group, one day can be submitted to RT.

Even though there is no control group and even with the short follow-up, assessing fatigue is an important clinical parameter that reflects several physical, functional, emotional and family aspects. It is expected that these results can contribute with the Oncology services, with the professionals involved with rehabilitation and also with prevention or therapeutic therapies for the potential pulmonary lesions, fatigue and physical and functional damage, once RT is still part of the complementary treatment for breast cancer.

CONCLUSION

It was observed that, in the short term, RT promoted a negative impact on pulmonary function, a significant increase in fatigue and the compromise of physical and functional well-being. However, no significant correlations were observed between pulmonary function, total radiation dose and fatigue.

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