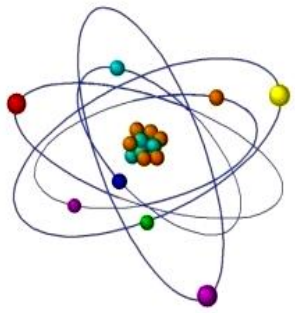
HEMORHEOLOGICAL AND MICROCIRCULATORY DYNAMICS DURING BREAST CANCER RADIOTHERAPY



Maia Mantskava*, Giorgi Kuchava, Nana Momtselidze

Iv.Beritashvili Experimental Center of Biomedicine, Georgia

DOI:10.63465/rrs6202611755 *Corresponding author: biomedicine.med@gmail.com

ABSTRACT**:** *Background. Radiation therapy is an essential component of multimodal breast cancer treatment. Despite its proven clinical efficacy, irradiation may induce vascular dysfunction, oxidative stress, microcirculatory disturbances, and alterations in blood rheology. Erythrocyte deformability and aggregation are key determinants of microvascular blood flow and tissue perfusion and may therefore serve as potential biomarkers of radiation-induced vascular impairment. Objective. To evaluate the dynamics of hemorheological parameters in patients with left-sided breast cancer during radiation therapy and assess their potential significance as markers of microcirculatory dysfunction. Materials and Methods. A prospective observational study included 42 patients with histologically confirmed left-sided invasive ductal breast carcinoma undergoing postoperative external beam radiation therapy. Seventeen age-matched healthy females served as controls. Radiation therapy was delivered using conventional fractionation with a daily dose of 2 Gy and a total focal dose of 45–50 Gy. Hemorheological parameters, including erythrocyte deformability and erythrocyte aggregation, were assessed before irradiation, on day 8, and on day 16 after initiation of treatment. Statistical analysis was performed using repeated measures ANOVA with post hoc pairwise comparisons. Results. Progressive deterioration of hemorheological parameters was observed during radiation therapy. Erythrocyte deformability significantly decreased from 1.86 ± 0.15 before treatment to 1.29 ± 0.18 after 16 days of irradiation ($p < 0.001$), whereas erythrocyte aggregation increased from 27.4 ± 2.1 to 36.9 ± 3.2 ($p < 0.001$). The most pronounced changes were detected after 16 irradiation sessions, indicating progressive impairment of blood rheology and microcirculatory function. Conclusion. Radiation therapy in patients with breast cancer is associated with progressive impairment of erythrocyte deformability and enhanced erythrocyte aggregation. These hemorheological disturbances may reflect early microcirculatory and vascular dysfunction during treatment. Monitoring hemorheological parameters may therefore provide additional information for early detection of radiation-associated vascular impairment.*

Keywords: breast cancer; radiation therapy; hemorheology; erythrocyte deformability

1. INTRODUCTION

Breast cancer remains one of the most prevalent malignancies among women worldwide and represents a major public health challenge. Advances in surgery, chemotherapy, hormonal therapy, targeted therapy, and radiation therapy have substantially improved patient survival

rates. Nevertheless, radiation therapy, despite its undeniable therapeutic benefits, may induce early and late vascular alterations associated with endothelial dysfunction, inflammatory activation, oxidative stress, and impaired microcirculation [1,2]. Microcirculatory homeostasis largely depends on the rheological properties of blood, particularly on erythrocyte deformability and aggregation. Erythrocyte deformability is essential for adequate capillary perfusion because red blood cells must undergo significant shape changes while passing through narrow microvessels. Simultaneously, excessive erythrocyte aggregation increases blood viscosity and contributes to impaired tissue perfusion and local hypoxia [3]. Ionizing radiation is known to induce oxidative damage to membrane lipids and cytoskeletal proteins, leading to impaired mechanical properties of erythrocytes [4,5]. These alterations may aggravate microvascular dysfunction and contribute to radiation-associated tissue injury. Therefore, investigation of hemorheological changes during radiation therapy may improve understanding of the mechanisms underlying radiation-induced vascular impairment and may help identify early biomarkers of microcirculatory dysfunction. This study aimed to assess changes in erythrocyte deformability and aggregation in patients with left-sided breast cancer during radiation therapy.

MATERIAL AND METHODS

2.1 Study Design

A prospective observational study was conducted in patients with left-sided breast cancer undergoing postoperative radiation therapy.

2.2 Patients and Control Group Characteristics

The study included 42 female patients with histologically confirmed left-sided invasive ductal breast carcinoma treated according to contemporary clinical guidelines. Seventeen age-matched, practically healthy females without oncological, hematological, inflammatory, or severe cardiovascular diseases were included in the control group. All participants provided written informed consent before enrollment in the study.

2.3 Inclusion and Exclusion Criteria

In our studies, we included female patients with a confirmed diagnosis of left-sided breast cancer, standard radiation therapy, and the absence of severe hematological disorders. All patients signed informed consent. In our studies, we excluded female patients with severe cardiovascular disease, decompensated diabetes mellitus, acute inflammatory diseases, and hematological disorders affecting blood rheology.

2.3 Radiation Therapy

Radiation therapy was delivered according to standard protocols for postoperative left breast irradiation using conventional fractionation schedules with a daily dose of 2 Gy and a total focal dose of 45–50 Gy.

2.5 Hemorheological Assessment

Blood samples were collected at three stages: before radiation therapy (Group A); on day 8 after initiation of irradiation (Group B); on day 16 after initiation of irradiation (Group C).

Blood hemorheology was assessed by measuring erythrocyte deformability and erythrocyte aggregation. Erythrocyte deformability was evaluated using the filtration method based on the Reid principle [6]. Erythrocyte aggregation was assessed using a texture analysis system (Laitz, Germany) employing the "Georgian technique" [7], the validity of which was previously confirmed using in silico methods [8].

2.6 Statistical Analysis

Statistical analysis was performed using SPSS Statistics software (IBM Corp., USA). Data are presented as mean ± standard deviation (M ± SD). Normality of data distribution was assessed using the Shapiro–Wilk test. Differences between repeated measurements obtained during radiation therapy were analyzed using repeated measures analysis of variance (repeated measures ANOVA) followed by Bonferroni post hoc analysis. Comparisons between patients and controls were performed using the independent Student's t-test. Differences were considered statistically significant at $p < 0.05$.

3. RESULTS

3.1 General Characteristics of the Study Population

A total of 42 patients with left-sided breast cancer were included in the study. The mean age was 56.3 ± 7.8 years. All patients underwent standard external beam radiation therapy. Descriptions of patients can be seen in Table 1.

Table 1. General Characteristics of Patients

Parameter		Value
Number of patients		42
Number of control group		17
Mean age in patients group, years		56.3 ± 7.8
Mean age in control group		54.2 ± 8.2
Left-sided localization		42 (100%)
Standard radiation therapy	(8 days)	42 (100%)
	(16 days)	42 (100%)

3.2 Data of investigate of Patients and Control groups

For ease of understanding, we will designate the group of patients with breast cancer according to treatment as Group A. After irradiation of the same patients after 8 days, we will designate it as Group B. After irradiation of the same patients after 8 days, we will designate it as Group C. Details of data can be seen in Table 2 and Table 3. Comparative analysis of hemorheological parameters demonstrated progressive deterioration of erythrocyte functional properties during radiotherapy in patients with breast cancer. In Group A (before treatment), the erythrocyte deformability index was significantly lower than in healthy controls (1.86 ± 0.15 vs 2.10 ± 0.12; $p < 0.001$). Simultaneously, erythrocyte aggregation was significantly increased compared with the control group (27.4 ± 2.1 vs 23.0 ± 1.8; $p < 0.001$), indicating impaired rheological properties of blood and microcirculatory disturbances already present before treatment. In

Group B (after 8 irradiation sessions), a significant worsening of hemorheological parameters was observed. The erythrocyte deformability index decreased to 1.54 ± 0.17, which was significantly lower than both the control group and Group A ($p < 0.001$). At the same time, erythrocyte aggregation increased to 31.8 ± 2.7 ($p < 0.001$), reflecting enhanced erythrocyte interaction and increased blood viscosity during radiotherapy. The most pronounced alterations were detected in Group C (after 16 irradiation sessions). The erythrocyte deformability index further declined to 1.29 ± 0.18, whereas erythrocyte aggregation increased to 36.9 ± 3.2. These changes were statistically significant compared with both Group A and Group B ($p < 0.001$). Thus, radiotherapy in patients with breast cancer was associated with progressive impairment of erythrocyte deformability and enhancement of erythrocyte aggregation, suggesting aggravation of microcirculatory and hemorheological disturbances throughout the treatment course.

Table 2. Dynamics of Hemorheological Parameters in Patients with Breast Cancer During Radiotherapy. M±STD. * p < 0.05 compared with control; ⊗ p < 0.05 compared with Group A; ⊕ p < 0.05 compared with Group B.

Parameter	Control	Group A	Group B	Group C	p
Erythrocyte deformability index	2.10 ± 0.12	1.86 ± 0.15*	1.54 ± 0.17*⊗	1.29 ± 0.18*⊗⊕	<0.001
Erythrocyte aggregation index	23.0 ± 1.8	27.4 ± 2.1*	31.8 ± 2.7*⊗⊕	36.9 ± 3.2*⊗⊕	<0.001

Table 3. Pairwise Statistical Comparisons

Comparison	Erytrocite Deformability Index t	Erytrocite Deformability Index p	Erytrocite Aggregation Index t	Erytrocite Aggregation Index p
Control vs Group A	5.42	<0.001	7.18	<0.001
Group A vs Group B	7.31	<0.001	8.04	<0.001
Group B vs Group C	6.18	<0.001	7.26	<0.001

DISCUSSION

The present study demonstrated progressive deterioration of blood hemorheological properties in patients with breast cancer during radiation therapy. Even before treatment initiation, patients exhibited significantly reduced erythrocyte deformability and enhanced erythrocyte aggregation compared with healthy controls, suggesting preexisting disturbances of microcirculation and blood rheology associated with malignant disease. Previous investigations have demonstrated that cancer-associated inflammation, activation of coagulation pathways, endothelial dysfunction, and elevated levels of fibrinogen and acute-phase proteins contribute substantially to hemorheological impairment in oncological patients [3,9]. The most pronounced alterations were observed during the course of radiation therapy. Erythrocyte deformability progressively decreased, whereas erythrocyte aggregation significantly increased after 8 and 16 irradiation sessions. These findings are consistent with current understanding of radiation-induced membrane injury and oxidative damage affecting erythrocyte mechanical properties. Ionizing radiation promotes excessive generation of reactive oxygen species, resulting in lipid peroxidation, protein oxidation, and cytoskeletal damage [4,5]. Experimental studies have shown that radiation exposure induces structural alterations in erythrocyte membranes and reduces cellular elasticity, thereby impairing microvascular blood flow [10]. Reduced erythrocyte deformability has important pathophysiological consequences because erythrocytes must undergo reversible deformation to pass through narrow capillaries. Loss of membrane elasticity impairs tissue perfusion, increases blood viscosity, and contributes to tissue hypoxia. Simultaneously, enhanced erythrocyte aggregation further aggravates microcirculatory disturbances by increasing flow resistance within the microvascular bed. The observed hemorheological disturbances may therefore represent early manifestations of radiation-associated vascular dysfunction. Monitoring erythrocyte deformability and aggregation during treatment could potentially facilitate identification of patients at increased risk of microcirculatory impairment and radiation-induced tissue injury. The present study has several limitations. First, the sample size was relatively small. Second, only short-term hemorheological changes during radiation therapy were evaluated, whereas long-term vascular outcomes were not assessed. Third, biomarkers of oxidative stress, endothelial dysfunction, inflammatory activation, and coagulation were not investigated. Therefore, further prospective studies with larger cohorts and prolonged follow-up are necessary.

CONCLUSION

Radiation therapy in patients with left-sided breast cancer is associated with progressive impairment of blood rheological properties. During treatment, erythrocyte deformability significantly decreases, whereas erythrocyte aggregation progressively increases. The most pronounced hemorheological alterations are observed after 16 days of radiation therapy. These disturbances may contribute to impaired microcirculation, tissue hypoxia, and radiation-

associated vascular dysfunction. Assessment of hemorheological parameters may represent a useful approach for early detection of microcirculatory impairment during radiation therapy.

Future Perspectives

Future investigations should include larger prospective cohorts and longer follow-up periods to evaluate the relationship between hemorheological disturbances and radiation-associated vascular dysfunction. Additional assessment of oxidative stress markers, endothelial dysfunction, inflammatory cytokines, and coagulation parameters may improve understanding of the mechanisms underlying radiation-induced microcirculatory impairment. Furthermore, studies evaluating antioxidant and hemorheological correction strategies could contribute to the development of individualized supportive therapy in breast cancer patients undergoing radiation treatment.

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