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# Efficacy of low-temperature argon plasma in the rehabilitation of patients undergoing radiation therapy for breast cancer

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#### **ABSTRACT**

**BACKGROUND:** During radiation therapy for breast cancer, healthy tissues are damaged, leading to both systemic and local reactions, including radiation dermatitis with such symptoms as erythema, dryness, peeling, and pain. Disturbances of the microcirculation lead to hypoxia and fibrosis. The use of low-temperature argon plasma is a promising method for preventing acute radiation-induced skin damage, which is crucial for maintaining quality of life, preventing complications, and minimizing long-term effects.

**AIM:** To evaluate the effectiveness of low-temperature argon plasma used in the complex medical rehabilitation of patients undergoing external radiation therapy for breast cancer.

**MATERIALS AND METHODS:** A prospective, randomized interventional study was conducted involving 60 breast cancer patients undergoing radiation therapy. All patients received a course of medical rehabilitation, including general magnetic therapy, exercise therapy, balance response training on a biofeedback simulator, nutritional support, and sessions with a medical psychologist. In the main group (n = 30), rehabilitation included low-temperature argon plasma treatment. Outcomes were assessed using the RTOG scale for acute complications of radiation therapy and laser Doppler flowmetry.

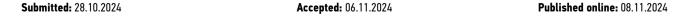
**RESULTS:** After completing radiation therapy and complex medical rehabilitation, statistically significant differences were observed between the main group and the comparison group (which did not receive low-temperature argon plasma treatment) in the severity of radiation reactions on the RTOG scale (p = 0.016) and in peripheral blood flow parameters.

**CONCLUSION:** Low-temperature argon plasma supports nutritional blood flow and active mechanisms for microcirculatory regulation, preserving skin blood supply and preventing severe acute radiation dermatitis.

**Keywords:** medical rehabilitation; low-temperature plasma; breast cancer; radiation therapy.

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# Результаты применения низкотемпературной аргоновой плазмы в реабилитации пациенток на этапе лучевой терапии рака молочной железы

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#### **RNUATOHHA**

**Обоснование.** Во время лучевой терапии рака молочной железы повреждаются здоровые ткани, вызывая общие и местные реакции, включая радиодерматиты с симптомами эритемы, сухости, шелушения и боли. Нарушения в микроциркуляторном звене ведут к гипоксии и фиброзу. Применение аргоновой низкотемпературной плазмы является перспективным методом для профилактики острых лучевых повреждений кожи, что важно для поддержания качества жизни, предотвращения осложнений и минимизации долгосрочных последствий.

**Цель исследования** — оценить эффективность применения низкотемпературной аргоновой плазмы в комплексной медицинской реабилитации пациенток на этапе дистанционной лучевой терапии рака молочной железы.

**Материалы и методы.** Проведено интервенционное проспективное рандомизированное исследование с участием 60 пациенток со злокачественными новообразованиями молочной железы, проходящих лучевую терапию. Все пациенты получали курс медицинской реабилитации: общую магнитотерапию, лечебную физкультуру, тренировки по опорной реакции на тренажёре с биологической обратной связью, нутритивную поддержку и занятия с медицинским психологом. У пациентов основной группы (*n*=30) в курс реабилитации были включены процедуры воздействия низкотемпературной аргоновой плазмы. Полученные результаты оценивались с помощью шкалы острых осложнений лучевой терапии RTOG и лазерной допплеровской флоуметрии.

**Результаты.** После курса лучевой терапии и комплексной медицинской реабилитации между основной группой и группой сравнения, в которой участники не получали процедур низкотемпературной аргоновой плазмы, зафиксированы статистически значимые различия в выраженности лучевых реакций по шкале RTOG (*p*=0,016), а также в показателях периферического кровотока.

**Заключение.** Низкотемпературная аргоновая плазма способствует поддержанию нутритивного кровотока и активных механизмов регуляции микроциркуляции, что обеспечивает сохранение трофики кожных покровов и профилактику развития тяжёлых острых радиодерматитов.

**Ключевые слова:** медицинская реабилитация; низкотемпературная плазма; рак молочной железы; лучевая терапия.

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# 低温<mark>氩等离子体在乳腺癌患者康复放射治疗阶段的应</mark> 用结果

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#### 摘要

**论证。**在乳腺癌放射治疗期间,健康组织会受到损伤,从而引起全身和局部反应,包括出现红斑、干燥、脱屑和疼痛症状的放射性皮炎。 微循环障碍会导致缺氧和纤维化。使用氩气低温等离子体是预防皮肤急性辐射损伤的一种很有前途的方法,对于生活质量的保持、并发症的预防和长期后果的最小化非常重要。

**研究目的** 一 评估低温氩等离子体在乳腺癌患者综合医疗康复中的远程放射治疗阶段的应用效果。

材料和方法。这项前瞻性干预随机研究涉及60名正在接受放射治疗的恶性乳腺肿瘤患者。 所有患者都接受了医疗康复疗程:普通磁疗、治疗性体能训练、生物反馈模拟器上的支持反 应训练、营养支持和医学心理学家课程。在主要治疗组的患者(n=30)中,低温氩等离子程 序也被纳入了康复疗程。使用RTOG放射治疗急性并发症量表和激光多普勒血流测量仪对结果 进行了评估。

**结果。**通过放射治疗疗程和综合医疗康复治疗后,主要治疗组和对比治疗组,其中参与者没有接受低温氩等离子体疗程,在RTOG量表中的辐射反应严重程度(p=0.016),以及外周血流指数方面均存在显著的统计学差异。

**结论。**低温氩等离子体有助于保持营养血流和微循环的积极调节机制,从而确保皮肤滋养性的保持和严重急性放射性皮炎的预防。

关键词: 医疗康复; 低温等离子体; 乳腺癌; 放射治疗。

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#### **BACKGROUND**

Radiation therapy is an essential component of breast cancer treatment. However, in addition to targeting malignant cells, it inevitably affects healthy tissues, leading to both systemic and local adverse effects [1, 2]. Radiodermatitis is the most common side effect of radiation therapy, typically presenting with erythema, dryness, peeling, and in some cases, severe pain. These manifestations can significantly reduce patients' quality of life and limit their daily activities [3]. Without proper prevention and timely management, radiation-induced skin reactions may progress to more serious complications, such as secondary infections due to disrupted skin integrity. This can result in interruptions in the radiation therapy course, ultimately compromising treatment efficacy [4]. Damage to the capillary network in healthy tissues and the release of inflammatory mediators trigger local inflammatory responses, exacerbate hypoxia, and subsequently initiate sclerotic processes that may lead to fibrosis of the surrounding structures [5, 6]. Timely and effective management of radiodermatitis is therefore critical for improving patients' quality of life and preventing delayed adverse effects.

One promising method for reducing the incidence and severity of acute radiodermatitis is low-temperature plasma [7], a partially ionized gas that contains reactive oxygen and nitrogen species in a gaseous state [8]. The safety and efficacy of plasma flows in various clinical applications, including oncology, are the basis for studies of its potential role in the prevention and treatment of radiation-induced skin injury [7, 9].

Thus, effective management of radiodermatitis during radiation therapy for breast cancer is essential to maintain patients' quality of life, prevent complications, ensure adherence to therapy, and reduce long-term sequelae [10].

**This study aimed** to evaluate the effectiveness of low-temperature argon plasma used in the complex medical rehabilitation of patients undergoing external radiation therapy for breast cancer.

# **METHODS**

#### Study Design

It was a prospective, randomized, interventional study involving 60 female patients undergoing external radiation therapy for breast cancer.

#### **Eligibility Criteria**

Inclusion criteria: Women aged 35–75 years with stage IIA, IIB, or IIIA breast cancer (ICD-10 codes C50.0–C50.9, malignant neoplasm of breast); history of polychemotherapy; currently undergoing adjuvant radiation therapy; and written informed consent to participate in the study, including consent to receive (or not receive) low-temperature argon plasma therapy as part of medical rehabilitation.

Exclusion criteria: Severe motor or coordination impairments, cognitive disorders, decompensated comorbidities, unexplained fever, type 1 or 2 diabetes mellitus, or refusal to participate in the study.

*Withdrawal criteria:* Participant's decision to withdraw, intolerance to physical therapy modalities, or non-adherence to treatment protocols and scheduled visits.

# **Study Setting**

The study was conducted at the clinic of the Federal State Budgetary Educational Institution for Continuing Professional Education Russian Medical Academy of Continuing Professional Education of the Ministry of Health of the Russian Federation (Prof. Yu.N. Kasatkin Clinic) from September 2022 to September 2024.

#### Intervention

Participants were randomly assigned (simple randomization) into two equal groups: main group (n=30) and reference group (n=30).

All participants received a standard rehabilitation program consisting of: therapeutic physical exercises (5 times/week), balance platform training with biofeedback (5 times/week), psychological counseling (3 times/week), nutritional support with a detox protein drink (200 mL, twice daily), general magnetotherapy (10 sessions, 5 times/week).

In addition, the main group received 10 sessions of low-temperature argon plasma therapy using the Plasma 200 device (ZAO Rudnev-Shilyaev, Moscow; Marketing Authorization No. RZN 2019/8192, dated March 11, 2019). Plasma was applied using a scanning technique over the postoperative scar and irradiated area at a 2–5 mm distance from the skin for 3 minutes, 5 times per week.

#### Main Study Outcome

The primary outcome was the effect of cold argon plasma on the severity of radiation-induced skin reactions during adjuvant radiation therapy, assessed by surrogate endpoints: severity of radiodermatitis and microcirculation parameters.

#### **Subgroup Analysis**

Participants were randomly assigned into two equal groups that were comparable in terms of age, tumor location, disease stage and histological type, prior treatment, and planned radiation therapy protocol.

#### **Outcomes Registration**

Participant evaluations were conducted on days 1–2 of admission for external radiation therapy (prior to the start of medical rehabilitation) and after completing the scheduled treatment. At each visit, patient complaints and physical examinations were documented, with special attention given to skin assessment for signs of radiodermatitis using the Radiation Therapy Oncology Group (RTOG) Acute Radiation Morbidity Scoring Criteria (1995): Grade 0 = no visible skin

changes; Grade 1 = follicular, faint or dull erythema, hair loss, dry desquamation, reduced sweating; Grade 2 = bright erythema, easy skin trauma, patchy moist desquamation, moderate edema; Grade 3 = confluent moist desquamation beyond skin folds, pitting edema; Grade 4 = ulceration, bleeding, or skin necrosis.

Capillary perfusion in irradiated zones was evaluated using the LAZMA-ST laser Doppler blood microcirculation analyzer (passport ID NAbX.941111.011  $\Pi$ C). Laser Doppler flowmetry measured changes in the microcirculatory-tissue system, including: M (microcirculation index),  $\delta$  (mean blood flow fluctuations), Kv (variability), shunting metrics (M<sub>nutr</sub>, M<sub>shunt</sub>, SI), activity of regulatory components: endothelial (Ae), myogenic (Am), neurogenic (An), cardiac (Ac), and respiratory (Ar).

Examinations were performed in a room at 24–25°C. Prior to starting measuremens, at least 2 hours had to pass after the last radiation session. Patients lay supine and acclimated for at least 10 minutes before measurement. The laser probe was placed 2 cm from the surgical scar or irradiated area (based on the treatment plan). For comparison, a symmetrical site on the non-irradiated side was measured similarly. Data were processed automatically using dedicated software.

#### **Ethics Approval**

All participants were informed about the purpose and objectives of the study, potential risks and obligations associated with participation, as well as the duration of the research. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki of the World Medical Association: Ethical Principles for Medical Research Involving Human Subjects.

The study protocol was approved by the local Ethics Committee (Protocol No. 13 dated September 27, 2022) of the Federal State Budgetary Educational Institution for Continuing Professional Education Russian Medical Academy of Continuing Professional Education of the Ministry of Health of the Russian Federation.

#### Statistical Analysis

Data were tested for normality using the Shapiro–Wilk test. Quantitative variables with a normal distribution were described using the arithmetic mean (M), standard deviations (SD), and 95% confidence intervals (95% CIs). Non-normally distributed data were described using the median (Me) and interquartile range (Q1; Q3). Group comparisons for normally distributed variables with equal variances were performed using the Student's t-test. Non-normally distributed variables were compared using the Mann–Whitney U test. Paired t-tests and Wilcoxon signed-rank tests were used for within-group comparisons of normally and non-normally distributed data, respectively. Differences were considered statistically significant at p < 0.05. The statistical analysis was performed using StatTech software, version 4.6.1 (StatTech, Russia).

# **RESULTS**

#### **Participants**

A total of 60 female patients undergoing adjuvant external radiation therapy for stage IIA, IIB, or IIIA breast cancer (C50.0–C50.9, malignant neoplasm of breast) after neoadjuvant polychemotherapy were included—30 in the main group and 30 in the reference group. At baseline, no signs of radiation-induced skin reactions were observed in either group (Grade 0 on the RTOG scale).

Laser Doppler flowmetry data of the postoperative scar region revealed no significant baseline differences between the groups (Table 1).

The amplitude-frequency spectrum analysis showed predominant neurogenic (An), endothelial (Ae), and myogenic (Am) oscillations in both groups, indicating active regulatory mechanisms. Shunt ( $M_{\rm shunt}$ ) and nutritive ( $M_{\rm nutr}$ ) blood flow, as well as the shunting index (SI), were comparable between groups.

## **Primary Results**

Following the scheduled radiation therapy and rehabilitation, radiodermatitis was observed in all participants. However, fewer Grade 2 reactions were noted in the group treated with low-temperature argon plasma (Table 2).

Statistically significant differences were observed in the severity of acute radiation-induced skin reactions between the main and reference groups (p=0.016) using Pearson's  $\chi^2$  test. In the main group, most patients either had no radiodermatitis or only grade 1, while in the reference group, grade 1 and 2 reactions predominated (Fig. 1).

Following completion of external radiation therapy, all groups exhibited changes in the microcirculatory system, including an increase in the mean tissue perfusion index (M) in the main group to 9.59 perfusion units [8.20; 10.97] and in the reference group to 8.75 perfusion units [7.35; 11.37] (p=0.487); a reduction in the standard deviation (δ) in the main group to 0.79 perfusion units [0.65; 0.87] and in the reference group to 0.61 perfusion units [0.44; 0.68] (p < 0.001); and a decrease in the coefficient of variation (Kv) in the main group to 8.34% [6.99; 9.69] and in the reference group to 8.04% [6.42; 9.54] (p=0.647). These findings indicate that microcirculatory function worsened in all patients following radiotherapy. However, in the reference group, there was a statistically significant increase (p < 0.001) in shunt blood flow (M<sub>shunt</sub> 6.02 [5.25; 6.51]; SI 2.00 [1.60; 2.46]), whereas in the group treated with low-temperature argon plasma, a statistically significant increase (p < 0.001) in nutritive blood flow was observed (M<sub>nutr</sub> 5.01 [4.23; 5.84]; SI 1.29 [1.08; 1.79]) (Figs. 2–4).

Stagnation in microcirculation was supported by amplitude-frequency analysis, which revealed altered activity in nearly all regulatory components (Table 3).

The reference group showed signs of passive blood flow regulation—elevated respiratory (p < 0.001) and cardiac

**Table 1.** Comparison of laser Doppler flowmetry indicators of the main group and the comparison group before the start of the course of medical rehabilitation

Parameters -	Operated side			Unaffected side		
	Main group	Reference group	P	Main group	Reference group	р
M. perfusion units	7.75 [6.66; 9.08]	7.59 [6.25; 9.17]	0.734	9.34 [8.71; 10.37]	9.64 [7.65; 11.38]	0.929
δ. perfusion units	0.93 [0.79; 1.06]	0.89 [0.77; 1.06]	0.853	1.16 [0.94; 1.35]	1.00 [0.91; 1.25]	0.348
Kv. %	10.16 [7.71; 12.40]	10.18 [7.31; 12.21]	0.836	11.80 [8.82; 13.76]	10.53 [9.01; 12.51]	0.478
Ae. perfusion units	0.27 [0.24; 0.34]	0.29 [0.26; 0.32]	0.871	0.32 [0.28; 0.36]	0.30 [0.24; 0.37]	0.399
An. perfusion units	0.28 [0.25; 0.34]	0.29 [0.25; 0.34]	0.807	0.34 [0.28; 0.38]	0.34 [0.27; 0.42]	0.888
Am. perfusion units	0.26 [0.21; 0.35]	0.26 [0.24; 0.32]	0.923	0.33 [0.25; 0.39]	0.33 [0.27; 0.39]	0.983
Ar. perfusion units	0.18 [0.15; 0.23]	0.20 [0.15; 0.22]	0.912	0.18 [0.14; 0.22]	0.18 [0.15; 0.23]	0.625
Ac. perfusion units	0.26 [0.20; 0.30]	0.25 [0.21; 0.29]	0.911	0.26 [0.21; 0.29]	0.24 [0.18; 0.30]	0.722
M <sub>nutr</sub> . perfusion units	3.70 [3.17; 4.42]	3.82 [2.99; 5.22]	0.982	4.67 [4.12; 5.66]	4.72 [3.88; 5.88]	1.000
${\rm M}_{\rm shun}$ . perfusion units	3.94 [3.10; 4.71]	3.78 [2.90; 4.84]	0.935	4.52 [3.79; 5.56]	4.91 [3.76; 5.71]	0.802
SI. arbitrary units	1.17 [0.95; 1.43]	1.16 [0.98; 1.45]	0.842	1.09 [0.93; 1.23]	1.11 [0.91; 1.36]	0.756

(p<0.001) rhythms, and reduced myogenic amplitude (Am), indicating vasoconstriction, decreased  $M_{\rm nutr}$ , and increased shunting. At the same time, patients in the main group who received low-temperature argon plasma therapy demonstrated preserved amplitudes of active regulatory mechanisms (myogenic and endothelial) and maintained baseline amplitudes of respiratory rhythms. No significant intergroup differences were observed in contralateral control region microcirculation.

#### **Adverse Events**

No adverse events were recorded during the study.

#### DISCUSSION

### **Summary of Primary Results**

During radiation therapy for breast cancer, patients exhibited RTOG-grade skin changes corroborated by laser Doppler

Table 2. Analysis of the dynamics of the RTOG scale depending on the group

Group						
	Parameter	Before		After		p
		Number	%	Number	%	
Main	Grade 0	30	100.0	11	36.7	<0.001
	Grade I	0	0.0	15	50.0	
	Grade II	0	0.0	4	13.3	
Reference	Grade 0	30	100.0	2	6.7	<0.001
	Grade I	0	0.0	20	66.7	
	Grade II	0	0.0	8	26.7	
р		-	-	0.0	16	_

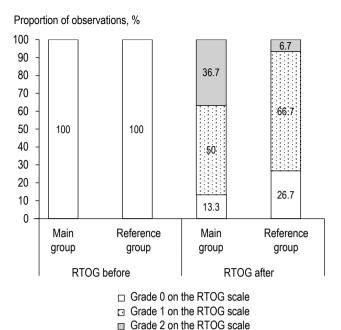
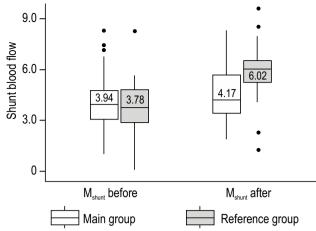


Fig. 1. Severity of radiation reactions according to the RTOG scale.

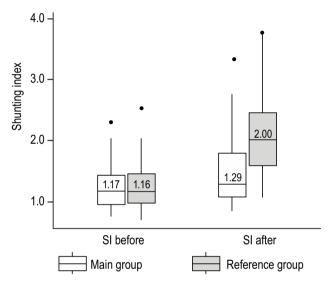
flowmetry findings. Typical alterations involved signs of stasis and hyperemia within the microcirculatory system, accompanied by impaired tissue trophism in irradiated areas. The application of low-temperature argon plasma as part of a comprehensive rehabilitation program helped sustain active mechanisms of blood flow regulation and preserved perfusion.

#### Interpretation

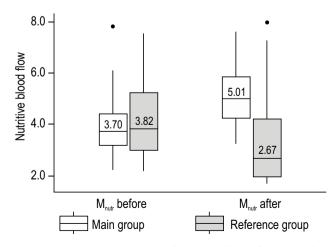
Post-treatment laser Doppler flowmetry revealed notable shifts in microcirculatory parameters in both study groups. All participants demonstrated increased local blood flow, coupled with decreased coefficient of variation and standard deviation of flow-indicative of diminished transcapillary exchange efficiency. Concurrently, elevated amplitudes of cardiac and respiratory rhythms suggested increased arterial inflow with impaired venular drainage, consistent with mixed venous-arterial hyperemia. The reference group also exhibited higher shunting, implying that more blood bypassed nutrient and oxygen exchange, as evidenced by a decrease in nutritive perfusion in the irradiated region. Together, these findings indicate reduced tissue oxygenation and nutrient delivery, fostering fibroblast activation and subsequent tissue sclerosis [11]. Conversely, patients receiving low-temperature plasma therapy maintained baseline nutritive perfusion and avoided dominance of passive regulatory mechanisms. These microcirculatory differences align with the statistically significant differences between the study groups in the severity of radiation-induced skin reactions, supporting the study's hypothesis regarding the efficacy of low-temperature plasma in preventing severe radiodermatitis [12]. The multimodal action of low-temperature plasma has already proven valuable in purulent surgery, dermatology, dentistry, and other areas, including oncology [13, 14]. Plasma flows



**Fig. 2.** Analysis of the dynamics of shunt blood flow depending on the group.



**Fig. 3.** Analysis of the dynamics of the bypass rate depending on the group.



**Fig. 4.** Analysis of the dynamics of nutritional blood flow depending on the group.

Table 3. Analysis of the dynamics of the amplitude of blood flow oscillations depending on the group

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Parameter -	Main	Reference	p p
Ae, perfusion units	0.29 [0.26; 0.32]	0.21 [0.16; 0.26]	<0.001
An, perfusion units	0.24 [0.21; 0.29]	0.22 [0.19; 0.25]	0.060
Am, perfusion units	0.22 [0.16; 0.27]	0.12 [0.09; 0.15]	<0.001
Ar, perfusion units	0.20 [0.18; 0.24]	0.21 [0.18; 0.27]	0.083
Ac, perfusion units	0.23 [0.19; 0.28]	0.24 [0.21; 0.28]	0.328
Contribution* e, Ae/σ	0.37 [0.31; 0.45]	0.35 [0.26; 0.48]	0.584
Contribution* n, An/σ	0.32 [0.27; 0.40]	0.39 [0.28; 0.49]	0.088
Contribution* m, Am/σ	0.27 [0.22; 0.38]	0.21 [0.17; 0.25]	0.017*
Contribution* r, Ar/σ	0.27 [0.20; 0.33]	0.37 [0.29; 0.58]	<0.001
Contribution* c, Ac/σ	0.31 [0.22; 0.38]	0.42 [0.29; 0.56]	0.002

Note. \* Contribution of endothelial (e), neurogenic (n), myogenic (m), respiratory (r), and cardiac (c) rhythms to blood flow regulation.

hold promise for medical rehabilitation, including the treatment of radiation-induced skin reactions [15, 16].

#### CONCLUSION

The rapid advancement of radiation therapy techniques has enhanced treatment capabilities, yet radiation-induced skin reactions remain a persistent challenge. These adverse effects can lead to infectious complications, fibrosis, pigmentation, and a decline in patients' quality of life. Low-temperature argon plasma contributed to the preservation of skin trophism in irradiated areas and reduced the severity of cutaneous radiation reactions, suggesting its potential as an effective prophylactic measure.

### ADDITIONAL INFORMATION

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**Competing interests.** The author's declare that they have no competing interests.

# ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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