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Use of an ozone - oxygen mixture in the treatment of cervical cancer: results of an efficacy and safety study

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Abstract: The aim of the study was to evaluate the effect of an ozone-oxygen mixture (OOM) as a radiomodifier in neoadjuvant chemoradiotherapy on the incidence of radiation-induced complications and treatment-related toxic effects, as well as on five-year overall survival in patients with stage IIb squamous cell cervical cancer. A retrospective comparative analysis was performed on 81 patients with stage IIb (T2bN0M0) squamous cell cervical cancer. Patients were divided into a study group (n=50), who received standard neoadjuvant chemoradiotherapy combined with transrectal insufflation of OOM, and a control group (n=31), who received standard neoadjuvant chemoradiotherapy without OOM. Neoadjuvant radiotherapy included external beam radiation therapy of 30 Gy (2 Gy per fraction) and intracavitary radiation therapy of 20 Gy (2 fractions of 10 Gy). Concurrently with radiotherapy, patients received monochemotherapy with cisplatin 40 mg/m² once every 7 days for 3 weeks (total dose 120 mg/ m²). Approximately 3 weeks after completion of neoadjuvant therapy, hysterectomy with adnexa and pelvic lymph node dissection was

performed; postoperative external beam radiotherapy was administered according to differentiated indications. In the study group, OOM was administered transrectally in a volume of 1500 ml after a cleansing enema prior to radiotherapy sessions. Results: The study group showed a statistically significant reduction in the incidence of radiation colitis (14.9% vs 29%; $p=0.046$) and radiation cystitis (4.3% vs 29%; $p=0.005$); no cases of radiation dermatitis were recorded. The incidence of hematological toxicity was lower in the study group (46% vs 58%; $p=0.005$). Five-year overall survival was 89.3% in the study group and 74.3% in the control group ($p<0.05$). Conclusion: The use of an ozone-oxygen mixture as an additional radiomodifier in neoadjuvant chemoradiotherapy is associated with a reduced incidence of certain radiation-induced complications and hematological toxicity, as well as improved five-year overall survival in the studied cohort.

Keywords: squamous cell cervical cancer, ozone-oxygen mixture, chemoradiotherapy, radiomodification, complications, survival

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Introduction. Cervical cancer (CC) remains a global public health challenge. In 2022, approximately 660-662 thousand new cases of CC and about 350 thousand deaths were recorded, ranking it fourth among cancers in women in terms of incidence [1, 2]. Around 83% of new cases and 88% of deaths occur in low- and middle-income countries [3, 4]. In the Russian Federation, 18,369 new cases were registered in 2022 (incidence rate of 17–18 per 100,000 female population) [5-7].

Radiation therapy (RT) is a key modality in the treatment of CC; however, its effectiveness is limited by the risk of damage to healthy tissues with dose escalation, as well as by several factors leading to local recurrence and metastasis [8-10]. To overcome radioresistance, the use of radiomodifiers is a promising approach [11]. Mechanisms of radiomodification include enhancement of oxidative stress, inhibition of DNA repair, modulation of apoptosis, and improvement of tumor oxygenation [12-14].

One of the approaches under investigation is the use of an ozone-oxygen mixture (OOM) to correct hypoxia in the tumor microenvironment [15]. This method exerts a complex effect on microcirculation and induces controlled oxidative stress, thereby increasing tumor radiosensitivity [16]. However, the clinical application of OOM requires further optimization of dosages, administration regimens, and safety assessment.

Objective. To evaluate the effect of an ozone-oxygen mixture as a radiomodifier in neoadjuvant chemoradiotherapy on the incidence of radiation-induced complications and treatment-related toxic effects, as well as on five-year overall survival in patients with stage IIb squamous cell carcinoma of the cervix.

Materials and Methods. Study design. A retrospective comparative cohort study was conducted. Treatment outcomes were analyzed in patients with stage IIb (T2bN0M0) squamous cell carcinoma

of the cervix who received neoadjuvant chemoradiotherapy followed by surgical treatment.

Sample characteristics. The study included 81 patients aged 24-63 years (mean age 42.6 ± 1.1 years) with histologically confirmed squamous cell carcinoma of the cervix, predominantly with exophytic tumor growth.

Group allocation. Patients were divided into two comparable groups: the study group ($n = 50$) received neoadjuvant chemoradiotherapy combined with transrectal insufflation of an ozone-oxygen mixture (OOM); the control group ($n = 31$) received neoadjuvant chemoradiotherapy without OOM.

All procedures involving patients were conducted in accordance with the principles of the Declaration of Helsinki and were approved by the Ethics Committee of Donetsk State Medical University of the Ministry of Health of Russia (Protocol № 14, dated 07.02.2022).

Neoadjuvant radiation therapy. All patients underwent combined radiation therapy: external beam radiation therapy (EBRT) with a total focal dose of 30 Gy using conventional fractionation (2 Gy per fraction), and intracavitary brachytherapy with a total focal dose of 20 Gy (2 fractions of 10 Gy).

Concurrent chemotherapy. Concurrent monotherapy with cisplatin was administered during radiation therapy: 40 mg/m² intravenously once weekly for 3 weeks (total dose 120 mg/m²). Cisplatin was used as a radiosensitizer.

Surgical treatment and postoperative therapy. Approximately 3 weeks after completion of neoadjuvant chemoradiotherapy, all patients underwent hysterectomy with adnexectomy and pelvic (iliac) lymph node dissection according to the standard technique. In the postoperative period, external beam radiation therapy and chemotherapy were administered based on specific indications (metastatic involvement of iliac lymph nodes, deep tumor invasion, low tumor differentiation

grade, presence of angiolymphatic and perineural invasion).

Radiomodification with OOM. An ozone-oxygen mixture was generated using the medical ozonator "Medozons-VM." At the preliminary stage, optimization of tumor oxygenation was performed (assessment of oxygenation parameters following intravenous administration of 0.9% saline solution bubbled with OOM, and transrectal insufflation of OOM with volumes of 500 mL, 1000 mL, and 1500 mL under instrumental monitoring of tumor tissue oxygen saturation). In the comparative clinical analysis, radiomodification was performed via transrectal insufflation of OOM: after a cleansing enema and prior to radiation therapy sessions, patients in the study group received slow transrectal administration of OOM at a volume of 1500 mL. OOM was not used in the control group.

Study endpoints. The following outcomes were assessed: (1) radiation-induced complications of neoadjuvant radiation therapy (radiation colitis, radiation cystitis, post-radiation dermatitis); (2) treatment-related toxic effects observed during neoadjuvant chemoradiotherapy, including hematologic disorders, gastrointestinal symptoms, flu-like syndrome, genitourinary disturbances, and cardiovascular reactions; (3) five-year overall survival.

Toxicity assessment. Treatment-related toxic effects were classified according to the CTC-NCIC scale (1991 version), graded from 0 to 4.

Assessment of radiation complications. Radiation complications were recorded as clinically verified adverse effects of radiation therapy.

Mathematical methods of data analysis. Data processing was performed using SPSS v.13.0. Quantitative variables were expressed as $M \pm m$, where M is the arithmetic mean and m is the standard error of the mean. Student's t -test was used for comparison of quantitative variables. Fisher's exact test was applied

for categorical variables. Survival rates were estimated using the Kaplan-Meier method with the Log-Rank test and Cox regression analysis. Differences were considered statistically significant at $p < 0.05$.

Results. Comparison of the types and incidence of complications associated with preoperative irradiation between the study groups demonstrated similar overall safety profiles. However, statistically significant differences were observed between the groups in the incidence of certain radiation-induced complications. The incidence of radiation colitis was 14.9% in the study group versus 29% in the control group ($p = 0.046$). The incidence of radiation cystitis was 4.3% in the study group and 29% in the control group ($p = 0.005$). No cases of post-radiation dermatitis were recorded in either group.

The tolerability of neoadjuvant chemoradiotherapy was assessed based on the frequency and severity of treatment-related toxic effects observed during therapy. The CTC-NCIC scale (1991 version) was used to classify toxicity grades (Table 1).

Analysis of the obtained data showed that most of the recorded adverse events were transient, and their severity was predominantly within grade 1-2 according to the commonly used toxicity grading scale, corresponding to CTCAE (Common Terminology Criteria for Adverse

Events). In most cases, these manifestations did not require specific medical intervention. However, in 5 patients (10% of the total), severe anemia was observed, requiring a comprehensive approach, including intensive pharmacotherapy and blood component transfusion.

In the control group, side effects were also predominantly transient and did not require specific intervention, similar to the study group. However, comparative analysis revealed a trend toward reduced hematological toxicity in the study group. Leukopenia was observed in 46% of cases in the study group versus 58% in the control group ($p = 0.005$; $p < 0.05$). The incidence of anemia was 66% and 71%, respectively, without statistical significance ($p > 0.05$). No cases of thrombocytopenia were recorded in the study group, in contrast to the control group.

A statistically significant difference was also observed in genitourinary complications: 60% in the study group versus 74.5% in the control group, supporting a local anti-inflammatory effect of the treatment. An increased incidence of gastrointestinal complications was noted in the study group (66% vs. 35.5% in the control group, $p = 0.005$), primarily in the form of acute gastritis. This finding is attributable to the implementation of more in-depth diagnostics, including mandatory endoscopic examination of the up-

per gastrointestinal tract in all patients. Thus, the higher proportion of diagnosed acute gastritis reflects improved diagnostic accuracy rather than increased treatment-related toxicity.

Analysis of other adverse effects associated with chemoradiotherapy, including flu-like syndrome and cardiovascular disorders, revealed no statistically significant differences between the groups ($p > 0.05$). The minimum follow-up period for patients was 0.2 years, the maximum was 5.7 years, with a mean of 2.7 ± 0.2 years. During the observation period, a total of 13 deaths were recorded in both groups (16% of all observations): 7 in the study group (8.6%) and 6 in the control group (7.4%). The obtained data indicate that the five-year overall survival rate was 89.3% in the study group and 74.3% in the control group. This difference was statistically significant ($t = 4.3$, $p < 0.05$), suggesting more favorable long-term treatment outcomes with the use of combined therapy (Fig. 1).

In the study group, deaths were recorded predominantly in the early period after treatment, whereas in the control group they occurred more evenly throughout the follow-up period. The overall five-year survival rate was 88.3% (data for patients with cervical cancer in the study groups). To assess the impact of clinico-morphological characteristics on survival, a mul-

Stratification of patients according to the type and severity of toxic effects in the study and control groups

Type of toxicity	Toxicity Grade						
	1 (study)	1 (control)	2 (study)	2 (control)	3 (study)	3 (control)	4 (study)
Gastrointestinal							
Diarrhea	8 (16)	7 (22.6)	-	-	-	-	-
Abdominal pain	14 (28)	5 (16.1)	4 (8)	2 (6.5)	-	-	-
Gastritis	28 (56)	10 (32.3)	5 (10)	1 (3.2)	-	-	-
Decreased appetite	-	1 (3.2)	-	-	-	-	-
Hematological							
Leukopenia	18 (36)	17 (54.8)	5 (10)	1 (3.2)	-	-	-
Anemia	22 (44)	10 (32.3)	6 (12)	10 (32.3)	4 (8)	2 (6.5)	1 (2)
Thrombocytopenia	-	1 (3.2)	-	1 (3.2)	-	-	-
Genitourinary							
Vaginitis	11 (22)	8 (25.8)	5 (10)	6 (19.4)	-	-	-
Cystitis (non-bacterial)	12 (24)	8 (25.8)	2 (4)	1 (3.2)	-	-	-
Flu-like syndrome							
Fever	1 (2)	1 (3.2)	2 (4)	1 (3.2)	-	-	-
Cardiovascular							
Elevated blood pressure	5 (10)	3 (9.7)	3 (6)	2 (6.5)	2 (4)	3 (9.7)	-
Arrhythmia	1 (2)	-	-	-	-	-	-
Hypotension	4 (8)	3 (9.7)	-	-	-	-	-
Venous	2 (4)	-	-	-	-	-	-

tivariate analysis was performed using the Cox proportional hazards model. The model included the following parameters: age, degree of therapeutic tumor pathomorphosis, presence of lymph node metastases, tumor differentiation grade, and the use of radiomodification during combined treatment.

The modeling results allowed the identification of combinations of parameters associated with different predicted values of overall survival. A higher predicted five-year survival corresponded to the following combination: older patient age (63 years), grade IV tumor pathomorphosis, absence of metastases in regional lymph nodes, high tumor differentiation (G1), and the use of ozone-oxygen mixture radiomodification in combined treatment (Fig. 2).

A lower predicted survival corresponded to the following combination: younger patient age (24 years), grade II tumor pathomorphosis, presence of metastases in regional lymph nodes, low grade of tumor differentiation, and absence of ozone-oxygen mixture (OOM) radiomodification (Fig. 3).

The rationale for the use of ozone therapy is based on the following key observations. First, cellular hypoxia has been recognized as a significant factor contributing to radioresistance [17]. Second, it has been established that malignant tumor cells may exhibit increased sensitivity to the effects of peroxides (e.g., hydrogen peroxide). Preliminary preclinical studies have shown that ozone can exert a destructive effect on the metabolism of cancer cells [18].

Experimental evidence also supports the presence of a direct antimetastatic and cytostatic effect of ozone. In cell cultures derived from lung, breast, and uterine tumors, ozone inhibited proliferation in up to 90% of samples. In studies conducted on mice with transplanted tumors, administration of an ozone-oxygen mixture resulted in an increase in survival by several tens of days compared to control values [19].

It is important to note that the sensitivity of different tumor types to ozone therapy varies. Existing *in vivo* models are limited, and clinical data remain scarce; however, promising results have been observed in terms of improved survival outcomes. Systemic administration of ozone exerts alternative mechanisms of action that are not directly associated with effects mimicking radiation or chemotherapy [20].

Study limitations. The study was conducted using a retrospective design and reflects the treatment outcomes of

patients who received therapy according to institutional protocols during the relevant period. Due to changes in clinical approaches and the content of clinical guidelines over time, the results should be interpreted as applicable to the studied cohort and the treatment regimens employed. Additionally, the grading of radiation-induced injuries according to the RTOG/EORTC scales was not assigned retrospectively, as the severity of radiation damage was not systematically documented in the primary records.

Conclusion. The use of an ozone-oxygen mixture (OOM) as an additional radiomodifier in neoadjuvant chemoradiotherapy is associated with a reduced incidence of certain radiation-induced complications and hematological toxicity, as well as with higher five-year overall survival rates in the studied cohort.

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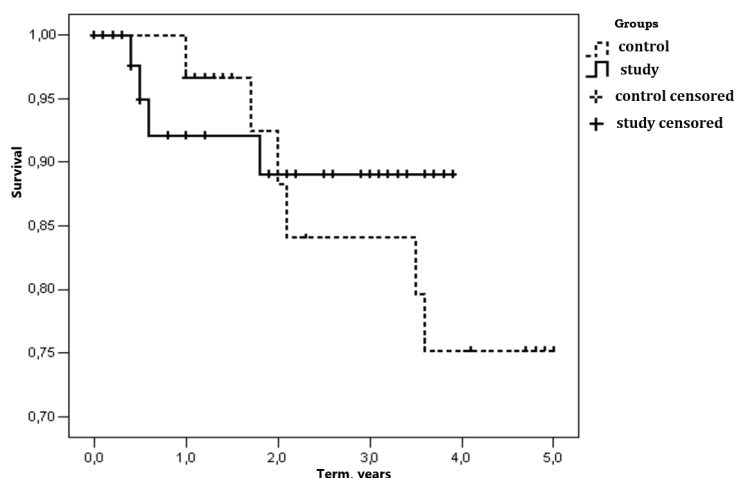


Fig. 1. Five-year survival results in the study groups

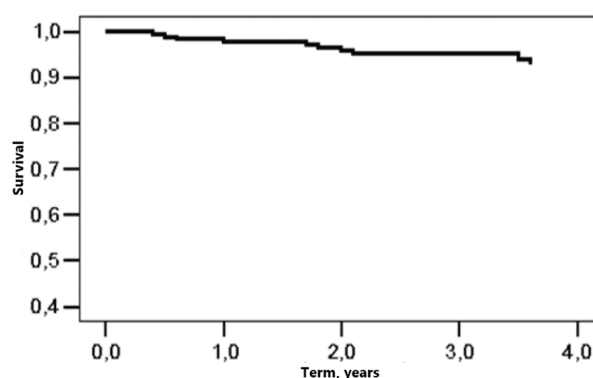


Fig. 2. Expected survival in a favorable prognosis

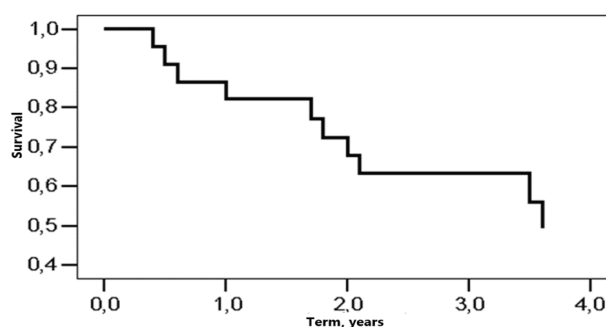


Fig. 3. Expected survival under an unfavorable prognosis

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