

# Radiodynamic Therapy with Chlorine-Based Photosensitizer on Pliss Lymphosarcoma Solid Tumor: *In Vivo* Experiment

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**Abstract:** The aim of this study was to investigate the antitumor efficacy of radiodynamic therapy (RDT) with a chlorine-based photosensitizer (PS) in an *in vivo* experiment.

**Material and Methods:** The study was performed in 35 white outbred rats weighing 180±30 g. Subcutaneously transplanted Pliss lymphosarcoma (PLS) was used as tumor model. Chlorin-based PS «Photolon» (RUE «Belmedpreparaty», Republic Belarus) was injected intravenously at a dose of 2.5 mg/kg. The radiation therapy sessions (RT) were carried out once 2.5–3 hours after the administration of the PS by the contact method on the device «microSelectron-HDR V3 Digital» (Elekta, Sweden) using  $\gamma$ -radiation (<sup>192</sup>Ir) in single focal doses (SFD) 2, 4 and 6 Gy. All laboratory animals were subdivided into 7 groups of 5 animals each: intact control, RT 2 Gy, RT 4 Gy, RT 6 Gy, PS + RT 2 Gy, PS + RT 4 Gy and PS + RT 6 Gy. The antitumor effectiveness of exposure was evaluated according to the indicators characterizing the dynamics of volume changes:  $V_{av}$  (cm<sup>3</sup>), the coefficient of absolute tumor growth (K, units) and the coefficient of tumor growth inhibition (TGI, %). The frequency of complete regressions (CR) was estimated 60 days after the performed exposures. In each group, the share of animals (%) with no visual and palpable signs of tumor growth was evaluated. The differences were considered statistically significant at the significance level of  $p < 0.05$ .

**Results:** On the 16<sup>th</sup> day from the beginning of the experiment  $V_{av}$  in groups were 39.07±4.19; 23.06±3.25 ( $p=0.012$ ); 35.04±2.35 ( $p=0.419$ ); 25.83±3.06 ( $p=0.027$ ); 28.36±3.45 (0.074); 25.47±1.88 ( $p=0.013$ ) and 16.56±3.64 cm<sup>3</sup> ( $p=0.002$ ), respectively. The K coefficients in the experimental groups were 1219.94; 657.86; 1296.78; 716.50; 833.12; 669.26 and 590.43 units, respectively. The TGI coefficients in the experimental groups were 40.98%; 10.31%; 33.89%; 27.41%; 34.81% and 57.61%, respectively. The frequency of complete tumor regressions 60 days after the start of the experiment was 0%, 20%, 0%, 0%, 0%, 0% and 40%, respectively.

**Conclusion:** RDT is a recent extension of conventional photodynamic therapy, in which visible/near infrared light irradiation is replaced by a well-tolerated dose of X-rays. Systemic administration of chlorine-based PS before the RT session increases the antitumor efficacy of RT in animals with PLS transplantable tumors. The data obtained indicate that further studies of the radiosensitizing properties of PS are promising.

**Keywords:** Chlorine-based photosensitizer, radiation therapy, radiodynamic therapy, laboratory animals, Pliss lymphosarcoma.

## INTRODUCTION

Radiation therapy (RT) is one of the three main treatments for patients with malignant neoplasms. As modifiers that selectively enhance sensitivity of tumor cells to ionizing radiation, various physical and chemical effects are used: hyperbaric oxygenation, local and general hypoxia, electron-acceptor compounds, artificial hyperglycemia, local and whole-body hyperthermia, etc. The use of radiomodifiers makes it possible to increase the radiosensitivity of tumor cells located in hypoxic zones of the tumor,

without increasing the degree of radiation damage to normal oxygenated cells.

Recently, the possibility of using photosensitizers (PS) as agents that increase the antitumor efficacy of RT has been actively studied. This area of scientific research in experimental oncology is called «Radiodynamic therapy» (RDT) [1, 2]. Scientists from centers in Japan, Germany and Lithuania have published the results of *in vitro* and *in vivo* experimental studies, which testify to the high antitumor efficacy of this method of treating malignant neoplasms [2-5]. This experimental study, performed on 35 rats with PLS transplanted tumors, is a continuation of the work, the results of which were presented in 2021 in our article [6].

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The aim of this study is to optimize the regimens of RT in combination with chlorine-based PS, as well as to study the antitumor efficacy of RDT using low doses of ionizing radiation.

## MATERIAL AND METHODS

### Laboratory Animals

The study was performed on 35 white random-bred rats of both sexes, obtained from the vivarium of the N.N. Alexandrov National Cancer Center of Belarus (Minsk, Republic Belarus) with a body weight of  $180\pm 30$  g, aged 2.5 months. The duration of quarantine before the inclusion in the experiment was 14 days. Rats were kept in standard conditions in terms of food and drinking rations, with a 12-hour lighting mode, at a temperature of  $18\text{--}22^\circ\text{C}$  and a humidity of 55–60% in cages with 5 individuals in each. The indicators of humidity, temperature and illumination in the room complied with the current sanitary rules for the device, equipment and maintenance of vivariums.

### Tumor Strain

The study used tumor strain Pliss lymphosarcoma (PLS) obtained from the Russian collection of cell cultures (Institute of Cytology of the Russian Academy of Sciences, St. Petersburg, Russian Federation).

### Tumor Model

The tumor model in rats was created by subcutaneous passivation *in vivo*. Subcutaneous grafting included the introduction of 0.5 ml of a 10% suspension of tumor cells in a 0.6% Hanks' solution subcutaneously in the left inguinal region. Rats with PLS were included in the experiment on the 7<sup>th</sup> day after the inoculation.

### Ethical Aspects

The experiments were conducted in accordance with the international legislation and the regulatory acts in force in the Republic of Belarus on conducting experimental studies with laboratory animals, namely The European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasbourg, France, dated 18.03.1986) and Directive 2010/63/EU of the European Parliament and of the European Union on the protection of animals used for scientific purposes (dated 22.09.2010). The study was reviewed and approved by the Ethics Committee of N.N. Alexandrov

National Cancer Center of Belarus (extract dated 25.02. 2022, № 180).

Rats were put under anesthesia (neuroleptanalgesia: 0.005% fentanyl solution + 0.25% droperidol solution, in a ratio of 2:1, 0.2 ml per 100 g of body weight, intramuscularly). After the end of the observation period for rats, they were put to death with generally accepted methods of euthanasia (aether pro narcosi) with the observance of humane methods of laboratory animals treatment.

### The Photosensitizer

Chlorine-based PS («Photolon») (RUE «Belmedpreparaty», Minsk, Republic Belarus), which is a trisodium salt of e6 chlorine with povidone K17 was used as a radiosensitizing agent. The PS was a lyophilized powder for the preparation of intravenous solution in the form of a porous mass of greenish-black color, 100 mg (registration № 16/11/886 of 08.11.2016). The PS was introduced by intravenous infusion in a darkened room at a dose of 2.5 mg/kg of body weight (according to the instructions for medical use).

### The Contact Radiation Therapy Session

RT was carried out once by the contact method on the device «microSelectron-HDR V3 Digital» (Elekta, Sweden) using  $\gamma$ -radiation ( $^{192}\text{Ir}$ ). To conduct RT on the area of the transplanted tumor, a «Leipzig» applicator was used, which was fixed on the tumor surface with soft rubber holders. The calculation of the radiation session time was carried out on the «Oncentra Brachy» planning system (Elekta, Sweden, version 4.5.2) on an empty series of images using the TG-43 algorithm without taking into account the reflection and scattering of radiation inside the applicator. Irradiation was performed in single focal doses (SFD) of 2, 4 and 6 Gy. The activity of the radiation source at the beginning of the experiments was 5.2 Ci. Irradiation was started 2.5–3 hours after the end of the PS infusion.

### The Design of the Research

All the treatments were performed after the tumor node reached the diameter of at least 5–6 mm: on the 7<sup>th</sup> day after PLS transplantation. The study was performed on 35 rats randomly distributed into groups of 5 animals each. The characteristics of the experimental groups are next: intact control (IC), RT 2 Gy, RT 4 Gy, RT 6 Gy, PS + RT 2 Gy, PS + RT 4 Gy and PS + RT 6 Gy, respectively.

### Criteria for Evaluating Antitumor Efficacy

The antitumor effectiveness of exposure was evaluated according to the indicators characterizing the dynamics of volume changes ( $V_{av.}$ ,  $\text{cm}^3$ ), the coefficient of absolute tumor growth (K, units) and the coefficient of tumor growth inhibition (TGI, %). The volume of tumors was calculated by the formula.

where

- $d_1$ ,  $d_2$ ,  $d_3$  are three mutually perpendicular diameters of the tumor (in cm);
- $\pi/6 = 0.52$  is a constant value;
- $V$  is the volume of the tumor (in  $\text{cm}^3$ ).

The absolute tumor growth coefficient (K) was calculated by the formula.

where

- $V_0$  is the initial volume of the tumor (before the introduction of the radiation session);
- $V_t$  is the volume of the tumor at a certain period of observation.

The coefficient of tumor growth inhibition (TGI) was calculated by the formula.

where

- $V_{\text{control}}$  – the average volume of the tumor in the control group (in  $\text{cm}^3$ );
- $V_{\text{experiment}}$  – the average volume of the tumor in the main group (in cm).

The dynamics of the growth of inoculated tumors was recorded starting from day 7 after the inoculation of the PLS for 2 weeks with an interval of 2-3 days.

The frequency of complete regressions (CR) was estimated 60 days after the performed exposures. In each group, the share of animals (%) with no visual and palpatory signs of tumor growth was evaluated [6].

### Statistical Data Processing

Statistical processing of data and graphical representation of the results were carried out with Excel 2010, Origin Pro (version 7.0) and Statistica (version 8.0) software. The results are presented in the form  $M \pm m$ , where  $M$  is the arithmetic mean and  $m$  is the error of the mean. To assess the reliability of the

differences, the Mann–Whitney U criterion was used. The differences were considered statistically significant at the significance level of  $p < 0.05$ .

### RESULTS

The experimental study was carried out on 35 rats LSP divided into 7 groups of 5 animals each. Rats of the control group were not injected with PS and did not undergo irradiation of tumors. At the beginning of the experiments, the  $V_{av.}$  did not differ statistically significantly in the groups ( $p > 0.05$ ). Data on the growth dynamics of transplanted tumors are presented in Table 1.

Irradiation in mono mode at SFD 2 and 6 Gy led to a statistically significant inhibition of LSP growth compared to IC ( $p = 0.012$ ;  $p = 0.027$ ; respectively), and in the case of SFD 4 Gy a tendency to inhibition was noted ( $p = 0.42$ ). The highest and almost identical antitumor efficacy of RT was demonstrated using 2 and 6 Gy ( $p = 0.55$ ).

Irradiation in the SFD 4 and 6 Gy after preliminary intravenous administration of the Ce6CPPPS at a dose of 2.5 mg/kg of body weight (RDT) led to a statistically significant inhibition of the growth of LSP compared with IC ( $p = 0.013$ ;  $p = 0.0019$ ; respectively), and in the case of application SFD 2 Gy showed a tendency to inhibition ( $p = 0.074$ ). There was no statistically significant difference between the combination therapy groups with SFD 2 and 4 Gy ( $p = 0.48$ ). The highest antitumor efficacy was demonstrated with the use of PS and subsequent irradiation at 6 Gy. The investigated indicator  $V_{av.}$  in this group was statistically significantly less than in other groups ( $p = 0.038$  – with PS + RT 2 Gy;  $p = 0.049$  – with PS + RT 4 Gy) (Figure 1).

Comparative assessment of indicators characterizing the dynamics of LSP growth showed a more pronounced inhibition of the growth of transplanted tumors in the group of RT 2 Gy compared to PS + RT 2 Gy ( $p = 0.29$ ), which indicates the absence of radiodynamic activity of chlorine-based PS. Comparative assessment of indicators characterizing the dynamics of LSP growth in the groups of RT 4 Gy and PS + RT 4 Gy registered statistically significant differences ( $p = 0.009$ ), which indicates the presence of radiodynamic activity of the chlorine-based PS during irradiation of tumors with 4 Gy. In a comparative assessment of the indicators characterizing the dynamics of LSP growth, in the groups of RT 6 Gy and

Table 1: Data on the Dynamics of Changes in the Linear Dimensions of Tumors in an Experiment on Rats with LSP

Groups	$V_{av.}, \text{ cm}^3 (M \pm m)$					
	K, units					
	TGI, %					
	p vs. intact control					
	Days after transplantation					
	5	7	9	12	14	16
IC	0.03±0.01	1.57±0.28	7.81±1.03	16.49±1.77	29.46±4.73	39.07±4.19
	—	48.06	243.06	514.31	919.63	1219.94
	—	—	—	—	—	—
	—	—	—	—	—	—
RT 2 Gy	0.04±0.01	0.96±0.07	2.96±0.15	9.02±1.38	15.34±2.77	23.06±3.25
	—	26.43	83.57	256.71	437.29	657.86
	—	38.85	62.10	45.30	47.93	40.98
	>0,05	0.058	0.0007	0.0067	0.026	0.012
RT 4 Gy	0.03±0.01	1.03±0.19	3.91±0.94	13.65±1.02	26.97±1.11	35.04±2.35
	—	37.15	143.81	504.56	997.89	1296.78
	—	34.39	49.94	17.22	8.45	10.31
	>0,05	0.139	0.017	0.192	0.618	0.419
RT 6 Gy	0.04±0.01	0.74±0.12	2.13±0.20	8.83±1,23	16.41±2.65	25.83±3.06
	—	19.56	58.17	244.28	454.83	716.50
	—	52.87	72.73	46.45	44.30	33.89
	>0,05	0.019	0.0002	0.0045	0.035	0.027
PS 2.5 mg/kg + RT 2 Gy	0.03±0.01	0.73±0.33	2.76±0.86	10.40±2.76	22.08±3.51	28.36±3.45
	—	20.47	80.18	304.88	648.41	833.12
	—	53.50	64.66	36.93	25.05	27.41
	>0,05	0.078	0.0031	0.091	0.236	0.074
PS 2.5 mg/kg + RT 4 Gy	0.04±0.01	0.84±0.11	1.93±0.54	9.41±0.94	19.22±1.46	25.47±1.88
	—	21.11	49.79	246.63	504.79	669.26
	—	46.50	75.29	42.94	34.76	34.81
	>0,05	0.034	0.0004	0.0047	0.063	0.013
PS 2.5 mg/kg + RT 6 Gy	0.03±0.01	0.54±0.15	1.27±0.23	5.44±1.14	12.98±3.31	16.56±3.64
	—	18.29	44.36	193.29	462.57	590.43
	—	65.61	83.74	67.01	55.94	57.61
	>0,05	0.0078	0.0001	0.0003	0.016	0.0019

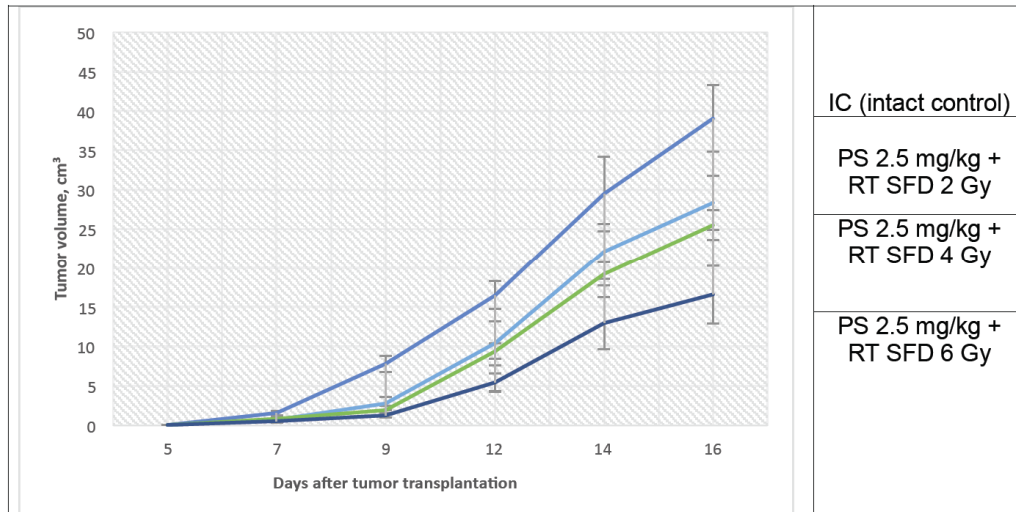
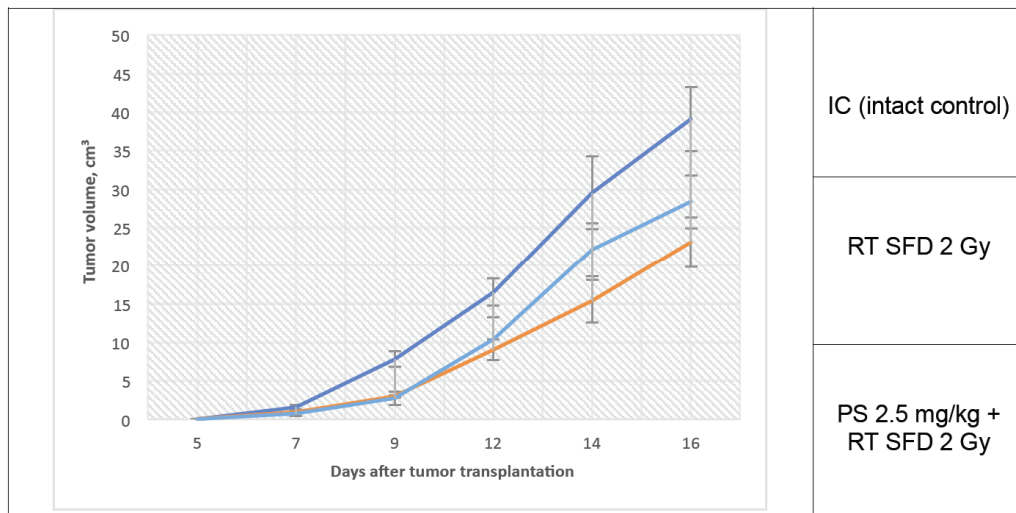
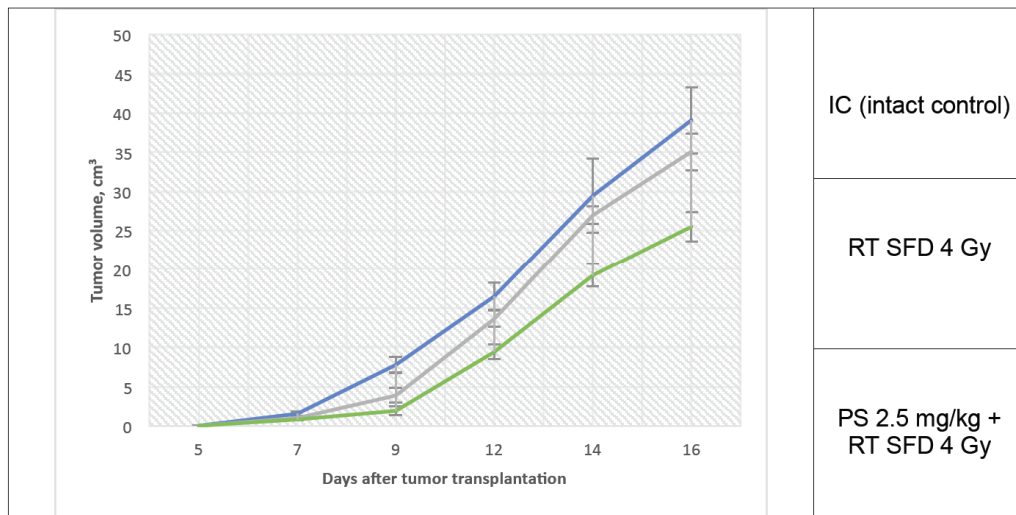


Figure 1: Antitumor efficacy of RDT (PS + RT in SFD 2, 4 and 6 Gy).

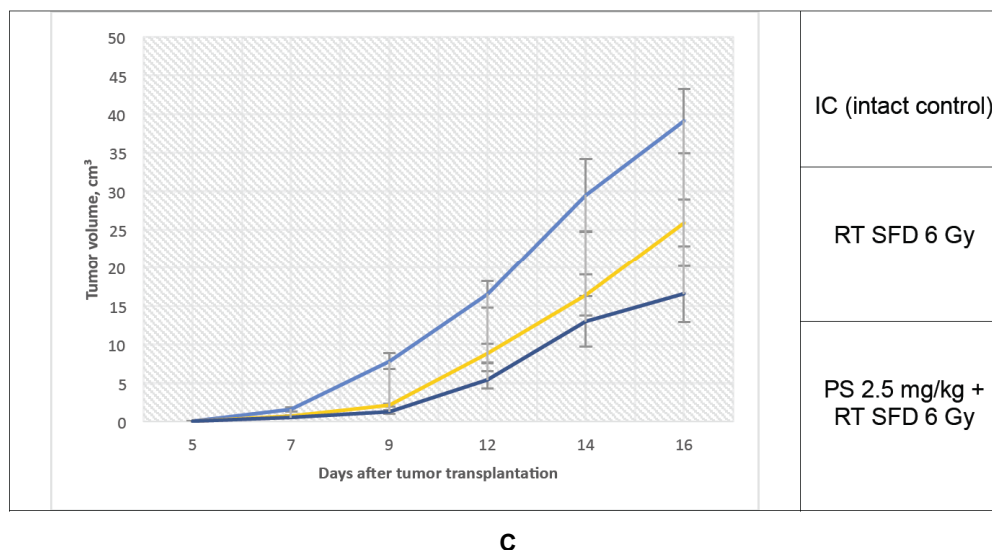


A



B

(Figure 2). Continued.



**Figure 2: A.** Antitumor efficacy of RDT in comparison with RT in mono mode;  $p=0.29$  (RDT vs. RT).

**B.** Antitumor efficacy of RDT in comparison with RT in mono mode;  $p=0.009$  (RDT vs. RT).

**C.** Antitumor efficacy of RDT in comparison with RT in mono mode;  $p=0.077$  (RDT vs. RT).

PS + RT 6 Gy, no statistically significant differences were registered, however, a tendency to inhibition was noted ( $p=0.077$ ), which indicates the presence of radiodynamic activity of the chlorine-based PS when irradiating tumors with 6 Gy. Graphical information is presented in Figure 2A, B, C.

## DISCUSSION

The method of photodynamic therapy (PDT) has been increasingly used in clinical practice [7]. Of particular interest are studies into the radiosensitizing properties of PS used in PDT. The first PS whose radiosensitizing activity was proved in experimental studies *in vitro* and *in vivo* were «Hematoporphyrin» and «Photofrin II» [8, 9, 10]. At the moment, researchers are especially interested in studying the radiosensitizing properties of 5-ALA which itself is not a PS, but it can be converted into a natural PS – protoporphyrin IX (PpIX) [1, 2, 3].

The mechanism of 5-ALA-RDT is as follows: exogenous 5-ALA induces the accumulation of PpIX in cancer cells, PpIX produces reactive oxygen species (ROS), mainly singlet oxygen, hydroxyl radical and superoxide anion, under ionizing radiation suitable for excitation of PpIX, which induces cellular damage and death [1, 2]. According to Shaffer M. *et al.*, other type of PS (for example, «Photofrin II»), when exposed to ionizing radiation, can enhance the radiolytic effect due to ROS formed in the tumor cell under the influence of radiation itself [11]. On the other hand, RT leads to

sublethal and lethal damage to tumor cells. Sublethal changes are usually reversible based on the mechanisms for restoring the functions of the tumor cell. In the case of activation of PS by ionizing radiation, the oligomeric components of this PS, interacting with intermediate free radicals (hydroxyl radicals) formed in the tumor cell during irradiation, prevent the development of these processes and, consequently, this combination creates antitumor effects [6, 11]

The experience of using various PS in combination with radiation therapy is systematized and analyzed in detail in our previous publications [6, 12]. The authors' teams have proved the radiosensitizing properties of PS on different tumor models. This fact is confirmed by a statistically significant increase in the number of dead tumor cells (*in vitro*: bladder cancer RT4, glioblastoma U-373 MG, glioma c6, gliosarcoma 9L, melanoma B16) and inhibition of the growth of transplanted tumors (*in vivo*: glioblastoma U-87 MG, bladder cancer RT4, Lewis sarcoma, hepatoma MH22) compared with RT in mono mode.

It is worth noting that the overwhelming majority of experimental studies is aimed at studying the antitumor effectiveness of the combined use of PS and remote RT. In the available literary sources, we found only one publication dedicated to the use of contact RT (brachytherapy). Morandi A. *et al.* presented the results of the combined use of PS «Photofrin II» at a dose of 3

mg/kg of body weight and contact RT. The model used was a solid form of mammary adenocarcinoma in linear BALB/c mice. Exposure to ionizing radiation was carried out 24 h after the completion of PS infusion, with SFD of 5 and 10 Gy. The authors reported that the results did not indicate any difference between the two groups (with and without the PS) after the brachytherapy. Therefore, contrary to other experiments reported in the literature, it can be concluded that the PS «Photofrin II» does not act as a radiosensitizer in adenocarcinoma tumors [13].

The relevance of the use of RDT in clinical oncology is confirmed by the fact that a number of pilot projects have been implemented on patients with malignant neoplasms of the brain, bladder, cervix, etc. [14-17].

## CONCLUSION

The pilot data obtained from the analysis of the immediate and long-term results of an experimental study on PLS transplanted tumors in rats indicate a pronounced tendency to a higher antitumor effect of combined treatment, including the use of PS followed by RT sessions at certain radiation doses, compared with RT alone. No experimental studies were found in the available literature sources that examine the effectiveness of the combined use of chlorine-type PS and ionizing radiation and demonstrating positive results, which brings us to the conclusion that more in-depth research in this direction is necessary and will be promising.

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The authors declare no conflict of interest.

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