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EIGHTH INTERNATIONAL CONFERENCE
ON RADIATION IN VARIOUS FIELDS OF RESEARCH
July 20-24, 2020 | Hunguest Hotel Sun Resort | Herceg Novi | Montenegro

Biological efficiency of a scanning proton beam under different irradiation modes in vitro

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Introduction

The use of a pencil beam scanning technology in proton therapy reduces the dose to patient healthy tissues and increases the uniformity of dose distribution in the tumor volume. It results also in more complex dose and LET distributions in irradiated volumes which may be field multiplicity, proton energy, tumor volume and localization specific. Emerging dose spots with elevated proton LET values throughout the target volume might cause the RBE variations in the tumor.

Purpose

To compare the biological effectiveness of the scanning proton beam with different ways of absorbed dose delivery to the irradiated volume by the clonogenic activity of Chinese hamster cells

Proton therapy:

- *tumor irradiation from several fields*
- *reduction of healthy patient tissue doses*
- *increasing the uniformity of dose distribution in the irradiated volume*

Distribution of linear energy transfer (LET) in the irradiated volume:

- *proton beam characteristics*
- *number of fields*
- *size of the irradiated volume and its localization*

Relative biological effectiveness (RBE) of protons is 1.1:

? *energy and LET of protons*

? *dose range*

? *normal or tumor cells*

Materials and methods

Proton Therapy Complex «Prometeus» (PROTOM, A. Tsyb Medical Radiological Research Centre, Obninsk

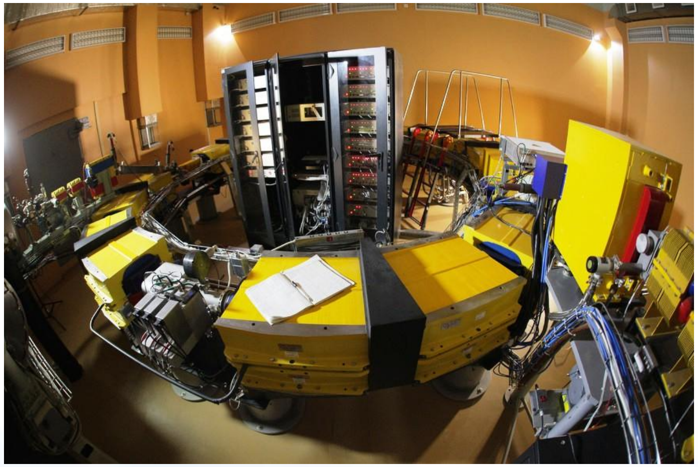
Beam characteristics:

- Pencil proton scanning beam – ø 4–7 mm
- Beam energy – 30–250 MeV
- Released beam intensity – $1 \cdot 10^9$ s^{-1}

Experimental conditions:

- Proton energy – 95.5–135.5 MeV
- Spread out Bragg peak – 1.5 cm
- Dose range – 2–10Gy

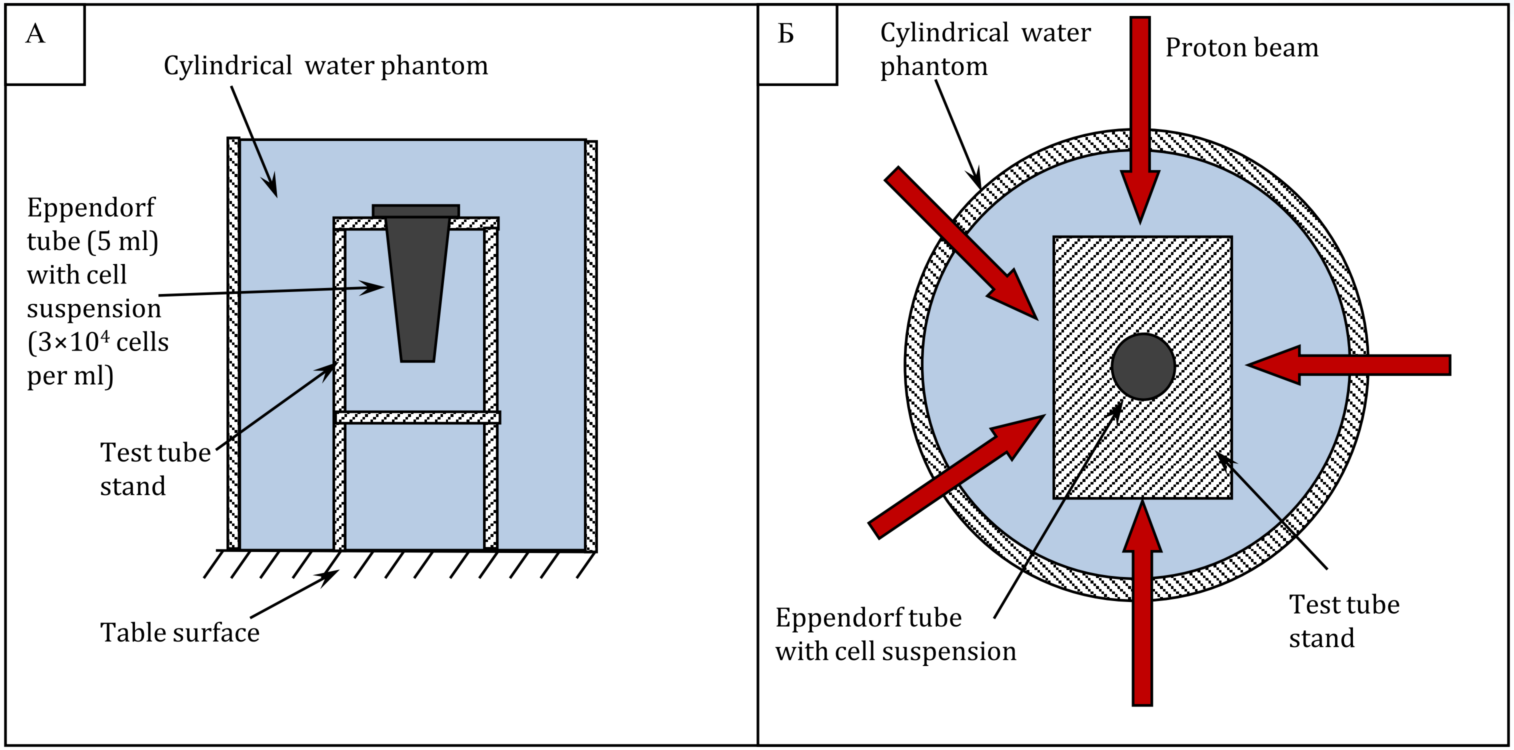
therapeutic room – position for radiobiological experiments implementation



synchrotron

Materials and methods

Scheme and modes of irradiation with a scanning proton beam



- The cells clonogenic activity test
- Chinese hamster V-79 fibroblasts and B14-150 fibrosarcoma cells in the stationary growth phase
- Ways of dose delivery to the irradiated volume:

  irradiation mode No 1 – single field, without dose fractionation
  irradiation mode No 2 – three fields (0°, 90°, 180°), without dose fractionation
  irradiation mode No 3 – single field, 2 Gy fractions in 30 s
  irradiation mode No 4 – five fields (0°, 90°, 180°,240°, 300°), 2 Gy fractions in 30 s

Materials and methods

Data analysis

The surviving fraction data were obtained from the mean of at least three independent experiments and fitted by a least squares method to Linear Quadratic (LQ) Model equation:

$$S = \exp(-\alpha D - \beta D^2).$$

where S is the surviving fraction, D (Gy) is the absorbed dose, α (Gy^{-1}) and β (Gy^{-2}) are the fitting coefficients. In terms of the TDRA (*Kellerer A.M., Rossi H.H.*) the linear component [$\exp(-\alpha D)$] might result from single-track events while the quadratic component [$\exp(-\beta D^2)$] might arise from two-track events. The α/β ratio is the dose at which the linear contribution to damage (αD) equals the quadratic contribution (βD^2).

Relative biological effectiveness (RBE) is defined as the ratio of a photon dose (D_γ) to a corresponding proton dose (D_p) resulting in the same biological effect (0.1 surviving fraction):

$$RBE = D_\gamma / D_p$$

Materials and methods

Data analysis

The RBE values were also calculated through the parameters of the regressions using the following formulas:

$$\mathrm{RBE}\left(\mathrm{LET}_d, D_p, [\alpha/\beta]_x\right) = \frac{1}{D_p}\left(\sqrt{\frac{1}{4}[\alpha/\beta]_x^2 + [\alpha/\beta]_x \, {}^{\alpha(\mathrm{LET}_d)}/_{\alpha_x} D_p + {}^{\beta(\mathrm{LET}_d)}/_{\beta_x} D_p^2} - \frac{1}{2}[\alpha/\beta]\right.$$

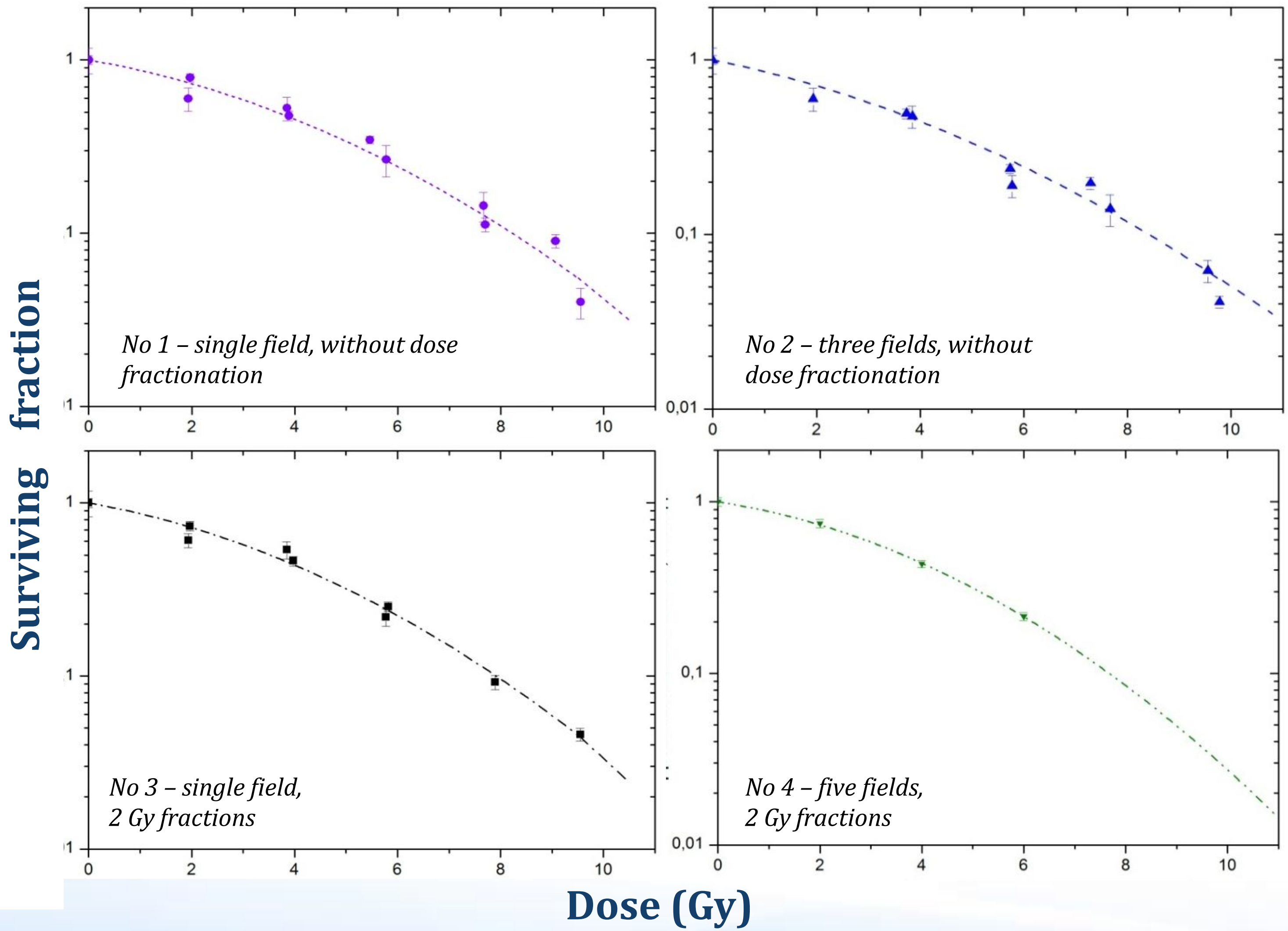
$$\mathrm{RBE}_{\max}\left(\mathrm{LET}_d, \alpha, \alpha_x\right) = {}^{\alpha(\mathrm{LET}_d)}/_{\alpha_x} \qquad \mathrm{RBE}_{\min}\left(\mathrm{LET}_d, \beta, \beta_x\right) = \sqrt{{}^{\beta(\mathrm{LET}_d)}/_{\beta_x}}$$

α_x, β_x describes dose-response to photons;
α, β are describes dose-response to photons;
LET_d – dose-averaged LET at the position of the biological sample
D_p – proton dose at which the proton RBE was defined;
RBE_{max} and RBE_{min} – the asymptotic values of RBE at doses of 0 and ∞ Gy, respectively

*Paganetti, H. Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer. 2014. Phys. Med. Biol. **59**:R419–R472*

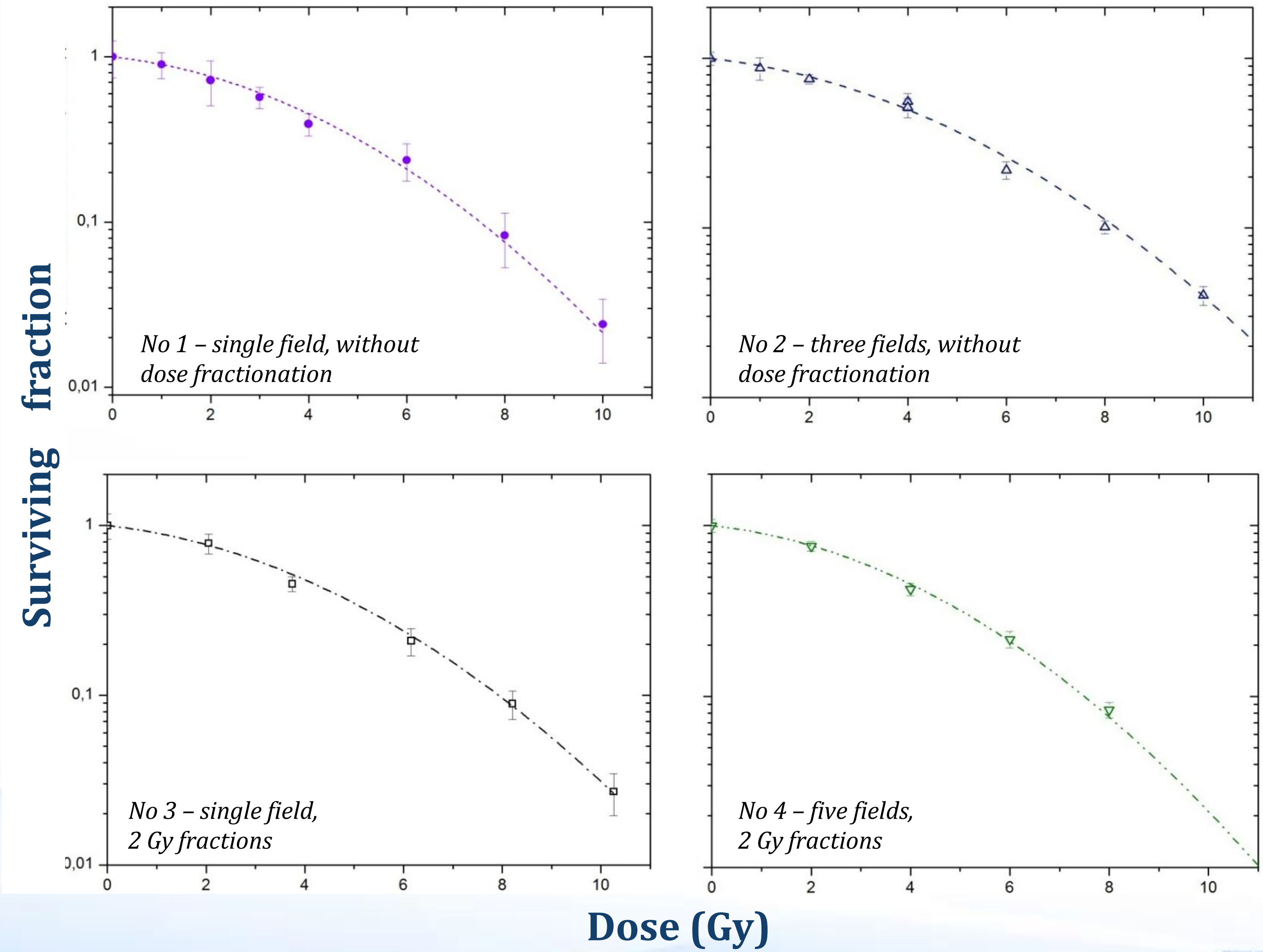
Results

The survival of V-79 cells following proton irradiation at the different ways of dose delivery



Results

The survival of B14-150 cells following proton irradiation at the different ways of dose delivery



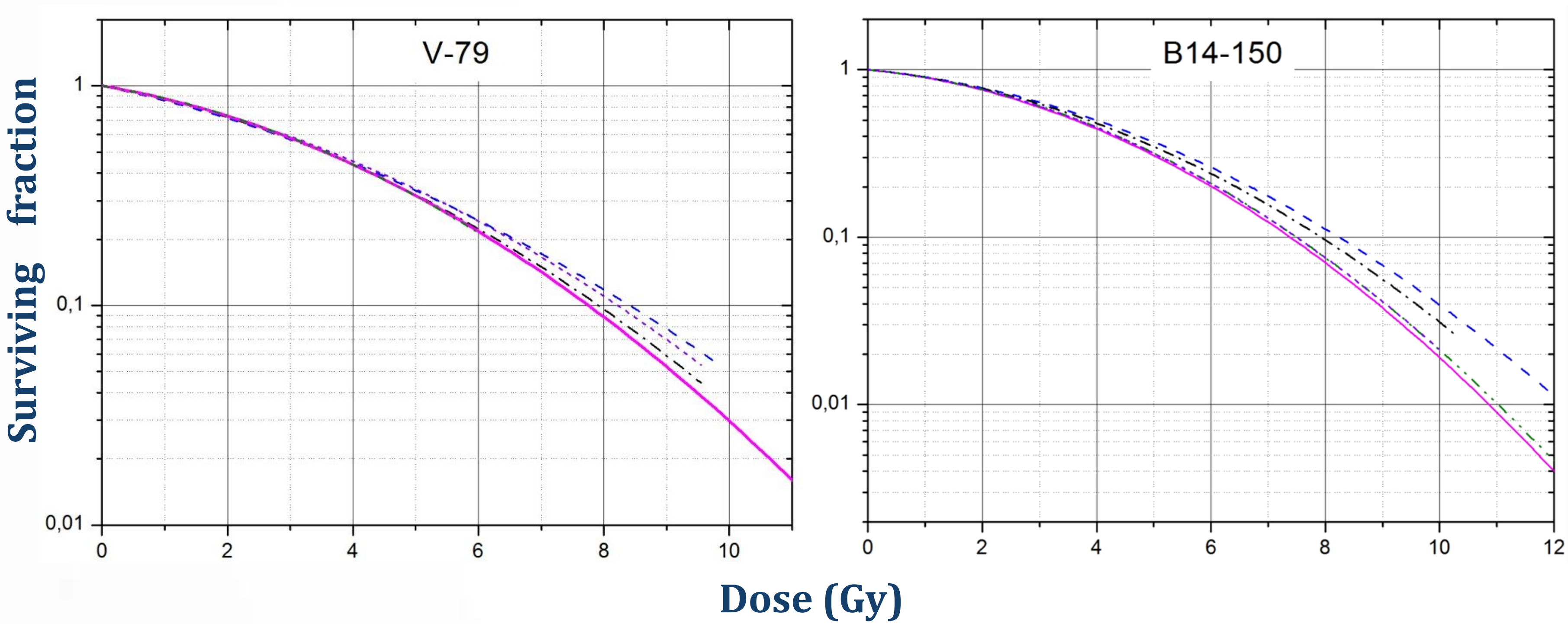
Results

Parameters of Linear-Quadratic model $S = \exp(-\alpha D - \beta D^2)$

Type and mode of irradiation	*V-79 fibroblasts*			*B14-150 fibrosarcoma*		
	α	β	R^2	α	β	R^2
γ-rays ^{60}Co	0.11±0.016	0.024±0.003	0.971	0.075±0.017	0.032±0.003	0.977
protons, No 1	0.12±0.015	0.019±0.002	0.978	0.074±0.016	0.031±0.003	0.989
protons, No 2	0.14±0.014	0.016±0.002	0.962	0.074±0.025	0.025±0.003	0.987
protons, No 3	0.12±0.018	0.021±0.003	0.990	0.075±0.016	0.027±0.005	0.998
protons, No 4	0.10±0.029	0.026±0.006	0.999	0.072±0.014	0.031±0.003	0.996

Results

The survival of V-79 and B14-150 cells following proton irradiation at the different ways of dose delivery



- - - - - – irradiation mode No 1

– – – – – irradiation mode No 2

– · – · – – irradiation mode No 3

– · · – · · – irradiation mode No 4

——— – γ-irradiation of ^{60}Co

Results

The RBE values for proton scanning beam at the different ways of dose delivery

V-79

Mode of irradiation	Level of the biological response					RBE_{max}	RBE_{min}
	surviving fraction 10 %	proton dose D_p (Gy)					
		2	6	10	15		
No 1	0.96	0.99	0.95	0.94	0.93	1.08	0.79
No 2	0.94	1.13	0.95	0.93	0.91	1.27	0.67
No 3	0.99	1.05	0.98	0.98	0.97	1.11	0.88
No 4	1.02	0.97	0.97	0.97	0.97	0.94	1.07

B14-150

Mode of irradiation	Level of the biological response					RBE_{max}	RBE_{min}
	surviving fraction 10 %	proton dose D_p (Gy)					
		2	6	10	15		
No 1	0.98	0.99	0.99	0.98	0.98	0.99	0.97
No 2	0.89	0.92	0.90	0.89	0.89	0.98	0.78
No 3	0.93	0.95	0.94	0.93	0.93	1.00	0.85
No 4	0.98	0.98	0.97	0.99	0.99	0.96	0.98

Conclusion

The RBE values differ slightly (about 10%) from the 1.1 adopted in radiation therapy. But they are consistent with it, if one takes into account the differences in the values of the absorbed doses planned and those measured by the ionization chamber (5–6%).

So, studies of the biological effectiveness of the scanning proton beam on Chinese hamster cells in vitro under different irradiation modes showed that the way of dose delivery to the irradiated volume does not significantly affect the irradiation result.

An increase of irradiation fields number and dose fractionation can be considered as a way to raise the uniformity of the dose distribution.

The experimental finding of the proton RBE values at the low and high dose ranges is important due to the inapplicability of the linear-quadratic model at such doses (the presence of hypersensitivity and induced radioresistance regions up to 1 Gy and a linear dependence above 10–12 Gy).

A detailed account of the dose distribution in the irradiated volume on LET is necessary to avoid a possible local increase of RBE in critical structures of tumors and normal tissues.

Thank you for your attention!

The study was supported by the Russian Foundation for Basic Research and the Government of the Kaluga Region as part of a scientific project No 18-44-400011