Survival of A549 cells after ultrahigh dose rate proton irradiation

Anna V. Rzyanina*, Gennady V. Mytsin, Alexey V. Agapov, Konstantin N. Shipulin, Eugenia A. Gritskova

Joint Institute for Nuclear Research, Dubna, Russia

https://doi.org/10.21175/rad.abstr.book.2024.40.1

Keywords: proton therapy, flash effect, ultrahigh dose rate irradiation

Flash radiotherapy is an innovative method of irradiation, which ensures the delivery of the therapeutic dose to the pathological focus in a time of about several tens of milliseconds. In this mode of irradiation, the degree of damage to normal tissues surrounding the tumor and falling under the influence of radiation decreases, at the same time, the effect on cancer cells remains almost at the same level, which improves the prospect of local control of the tumor with a lower frequency of side effects. To date, the exact radiobiological mechanisms underlying the flash effect are not fully clear.

A high-intensity proton beam with energy of 660 MeV was formed at the Phasotron accelerator of the Joint Institute for Nuclear Research, Dubna, designed to conduct radiobiological studies under flash therapy irradiation of cell cultures and small laboratory animals (mice, rats). The survival of A549 cells under proton beam irradiation in two modes, flash and standard was also compared. A difference in the survival of A549 cells irradiated in flash and standard modes was found. The magnitude of the flash effect is represented by the dose change factor (FID).

Aim: Comparison of cell survival under proton beam irradiation in flash and standard modes.

Materials and methods: *Cell culture:* Human lung carcinoma cells A 549. *Proton irradiation:* The irradiation of cells was carried out with the 660 MeV proton beam of the JINR Phasotron by the "shoot-through" technique in two modes: standard at a dose rate of 0.1 Gy/s and in flash mode at a dose rate of 70 Gy/s. Other beam parameters were the same. *Clonogenic survival.* Cells were seeded at the rate of 50 cells /ml after irradiation with protons at doses of 0, 1, 2, 4 and 6 Gy. 12-14 days after sowing, the number of grown colonies was calculated. The changes in the survival of cells under irradiation in two modes, standard and flash, were represented by survival curves.

Results: A slight difference was found in the survival rate of A549 cells irradiated in flash and standard modes. It should be noted that a statistically significant level of differences (*p <0.05) is manifested only at high doses of 4 and 6 Gy. In the dose range up to 2 Gy the error bands intersect, no statistically significant differences between the curves were found. Nevertheless, if we consider the general trend of all data points, it is clearly seen that proton irradiation at ultrahigh dose rates increases the survival rate of human lung carcinoma cells of the A 549 line compared to standard irradiation mode. The magnitude of the flash effect is represented by the dose rate coefficient (FID). The feed dose was defined as the ratio (instant dose)/(standard dose) for 10 % survival, for these studies the FID was 1.1. This value does not contradict the data of other research groups, where the FID was usually 1.1-1.5 [1]. Our results, namely, a higher survival rate under ultrahigh dose rate irradiation, are consistent with [2], but it should be noted that there are other results indicating no differences [3]. The presence of contradictory results requires further more detailed study in this field.

References:

1. J.D. Wilson, E.M. Hammond, G.S. Higgins, K. Petersson, Ultra-High Dose Rate (FLASH) Radiotherapy: Silver Bullet or Fool's Gold?, Front Oncol., 9, 1563, 2020.
2. Z.Guo, M. Buonanno, A. Harken G. Zhou, T. K. Hei, Mitochondrial Damage Response and Fate of Normal Cells Exposed to FLASH Irradiation with Protons, Radiation Research, 197,6, 569,2022.
3. S. Khan, M. Bassenne, J. Wang, R. Manjappa, S. Melemenidis, D.Y. Breitkreutz et al., Multicellular Spheroids as In Vitro Models of Oxygen Depletion During FLASH Irradiation, Int J Radiat Oncol., 110, 833, 2021.