Dose, dose-rate, beam-on time: what requisites for the “FLASH effect” ?

Vincent FAVAUDON, Charles FOUILLADE
Institut Curie, Inserm U 1021 - CNRS UMR 3347, Labs. 110-112, Centre universitaire, 91405 Orsay Cedex.
vincent.favaudon@curie.fr

With rare exceptions, today's anticancer radiation therapy facilities deliver mean dose-rates below 1 Gy/s and most clinical protocols involve daily fractions of 2 Gy cumulated for up to reaching a total dose limited by the tolerance of normal tissues. We recently investigated another methodology named “FLASH” that consists in delivering as much as 10-30 Gy of relativistic electrons in a single microsecond pulse, or else in a short (≤ 100 ms) sequence of microsecond pulses of 1-2 Gy each [1]. In mice FLASH was found to elicit a dramatic decrease of damage to normal tissues, with protection against vascular apoptosis and lung fibrosis [1] or memory loss after brain irradiation [2] whilst keeping the anti-tumor efficiency unchanged. Protection against normal tissue injury by FLASH has been confirmed in pig skin and in cat patients treated for sarcoma of the nasal planum [3]. Finally, the FLASH methodology requires facilities able to deliver large doses at ultrahigh dose rate, for which linear electron accelerators appear to be the most suitable technology at the present time. In our presentation we focus on the temporal and dose requirements for the FLASH effect to develop in normoxic tissues.

[1] Favaudon V, Caplier L, Monceau V, Pouzoulet F, Sayarath M, Fouillade C, *et al.* Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med. 2014;6:245ra93.
[2] Montay-Gruel P, Petersson K, Jaccard M, Boivin G, Germond JF, Petit B, *et al.* Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100Gy/s. Radiother Oncol. 2017;124:365-9.
[3] Vozenin MC, De Fornel P, Petersson K, Favaudon V, Jaccard M, Germond JF, *et al.* The advantage of Flash radiotherapy confirmed in mini-pig and cat-cancer patients. Clin Cancer Res 2018 (DOI 10.1158/1078-0432.CCR-17-3375).