Clinical Oncology 31 (2019) 405–406

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

FLASH Radiotherapy: The Next Technological Advance in Radiation Therapy?

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Received 15 May 2019; accepted 15 May 2019

FLASH radiotherapy involves the ultra-fast delivery of radiation treatment at dose rates several orders of magnitude greater than those currently in routine clinical practice. In order to eradicate tumours, all cancerous cells must be killed with normal tissue being spared from radiation damage as much as possible. Ultra-fast dose rates allow normal tissue tolerance levels to be exceeded, at least in animal models, with a greater probability of tumour control and little or no normal tissue damage.

This issue of *Clinical Oncology* contains a review of the biological benefits of ultra-high dose rate radiotherapy by Vozenin and colleagues [1]. A remarkably large amount of information is packed into this short and well-written review. Experimental data from a variety of *in vitro* cell and tissue culture models, supplemented more recently by animal studies, show that ultra-fast delivery of radiotherapy (in excess of 40 Gy/s) leads to sparing of normal tissues when compared with normal dose rates (about 0.03 Gy/s). One of the most striking animal studies listed is the treatment results of cats suffering from a spontaneous squamous cancer of the nasal plenum after FLASH irradiation. While under anaesthetic these animals were treated with a single fraction of 25–41 Gy to treatment volumes of 6–25 ml. Despite the high single doses used, dose-limiting toxicity was not seen, with only minimal or mild mucosal or skin acute effects that did not impair the animals' ability to eat. The tumour control probability was high compared with historical results, with a rate of 84% at 1 year, without any observed late effects.

As well as summarising other experimental results, some of which date back over 50 years, reasons are given why normal tissue is spared compared with cancers. One mechanism is the prevention of cytokine activation, such as the release of transforming growth factor-beta, which is not initiated in normal lung following FLASH irradiation. Another, and more likely mechanism, concerns the role of oxygen. FLASH radiation consumes all available oxygen and liberates significantly more electrons, resulting in many more ionisation events than at conventional dose rates. This maximises the differences in redox metabolism (reduction–oxidation reaction) and free radical chemistry between cancers and normal tissue. FLASH radiotherapy seems more effective in killing hypoxic cancerous cells than standard dose rate radiotherapy with the added advantage of sparing normal tissue.

Currently, few devices are available to deliver ultra-high dose radiotherapy, but preclinical devices specifically designed to treat humans are being installed in the USA and Europe. Some of the biological advantages of ultra-fast dose rates may be reduced by volume effects leading to the dispersal of scanned beams reducing oxygen consumption rates. Currently, the most advanced linear accelerator that can deliver ultra-high dose rates is a modified ELECKTA Precise machine developed by investigators from the University Hospitals of Skane and Lund in Sweden [2]. Fine tuning is still required to reduce variation in dose delivery and beam flatness, but it is estimated that the machine may be ready to treat humans in 3–5 years [3]. FLASH radiotherapy may be extended beyond photon treatment. Among others, the Institut Curie has developed a FLASH proton irradiation system for small animals [4]. Moreover, very recently, the University Medical Centre Groningen in the Netherlands modified one of two proton gantry treatment rooms to deliver dose rates of over 33 Gy/s [5].

Hard on the heels of once new techniques that have now become common place, such as intensity-modulated radiotherapy, image-guided radiotherapy and stereotactic ablative radiotherapy, FLASH radiotherapy clinical trials using photons or even protons may start in the next few years.

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https://doi.org/10.1016/j.clon.2019.05.011

Conflict of interest

The authors declare no conflict of interest.

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