Brazilian Journal of Oncology

Evolving radiation oncology techniques in the 21st century: the FLASH technique

A técnica FLASH: evolução das técnicas de radiação oncológica no século XXI

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ABSTRACT

Radiation therapy (RT) uses high doses of high energy X-rays to kill cancer cells. Fractionation and volume optimization were the main methods used to increase the dose given to the tumor and reduce the dose and side effects to the normal tissues (NT). Conventional RT works with dose rates up to 0.1 Gy per second. Opportunities to improve the biological efficacy of RT have been explored and options involving dose rate modulation are now available. Preclinical studies showed a drastic reduction in NT toxicity with preserved anti-tumor efficacy when using FLASH RT, furthermore this method enables higher doses to be given to the tumor. We reviewed the principles of FLASH RT.

Keywords: Toxicity; Radiation dosage; Free radicals; Oxidation-reduction; Adverse effects.

RESUMO

A terapia de radiação (TR) utiliza altas doses de raios X de alta energia para matar células cancerígenas. O fracionamento e a otimização do volume foram os principais métodos utilizados para aumentar a dose administrada ao tumor e reduzir a dose e os efeitos colaterais aos tecidos normais (TN). A TR convencional funciona com taxas de dose de até 0,1 Gy por segundo. Oportunidades para melhorar a eficácia biológica da TR foram exploradas e agora estão disponíveis opções envolvendo modulação da taxa de dose. Estudos pré-clínicos mostraram uma redução drástica da toxicidade em TN com eficácia antitumoral preservada ao usar o FLASH RT; além disso, esse método permite que doses mais altas sejam dadas ao tumor. Revisamos os princípios do FLASH RT.

Descritores: Toxicidade; Dosagem de radiação; Radicais livres; Redução de oxidação; Efeitos adversos.

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Financial support: none to declare.
Conflicts of interest: The authors declare no conflict of interest relevant to this manuscript.
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Received on: January 14, 2020 | **Accepted on:** March 6, 2020 | **Published on:** June 10, 2020
DOI: https://doi.org/10.5935/2526-8732.20200012

INTRODUCTION

Conventional radiation therapy (RT) is one of the three main forms of cancer treatment. RT uses high doses of high energy X-rays, electrons or charged particles to kill cancer cells and works with dose rates up to 0.1 Gy per second. One of the problems still to be solved in RT is related to the tolerance of normal tissues (NT) surrounding the tumor.[1] In fact, NT injury dictates the maximum tolerated dose that can be safely delivered and the ability to spare the NT from harmful effects of RT has being studied since its discovery around 100 years ago. Fractionation and volume optimization were the main methods used to increase the dose given to the tumor and reduce the dose and effect to the NT.

In the last two decades, advances in high-precision treatment delivery and multimodal imaging integrated to the linear accelerators (image guided radiotherapy), volumetric-modulated, or particle-based RT approaches have improved tolerance to conventional RT (cvRT),[2] increasing significantly the rate of patients cured and free of recurrences. Despite the advances cited above, the ability to protect NT remains a significant clinical challenge in RT. To further optimize RT promising options are coming from targeted therapies and biomodulatory agents.[3,4]

The use of different fractionation form 1.8 to 2.0 Gy have been introduced in the clinic very slowly because of the "linear quadratic model" that pointed to the benefits of minimizing the dose per fraction, so as not to induce severe late effects.[5] In the last decades advances in image guided brachytherapy and stereotactic ablative RT using various different dose rates have been successful for treating some tumors, revealing the benefits of using lesser fractions of doses in excess of 2 Gy.

Of course, many other opportunities to improve the biological efficacy of RT have been explored and options involving dose rate modulation were studied for more than 40 years, but they were not able to be incorporated in the daily clinical practice due to limited technology of radiation equipments on giving higher dose rates.

FLASH RT and normal tissue response

RT has a vastly range of dose rates and the conventional dose-rate range from 0.07 to Gy per second. The evolution of equipments able to delivery of doses at dose rates higher than those currently used in routine clinical practice at the biological level permits the reduction of normal tissue induced toxicity and this has been named the FLASH effect. The ultra-rapid dose delivery leads to shorter time of exposure to X-rays, resulting in a relative protection of various normal tissues when they are exposed to single doses of FLASH RT. Another clear clinical advantage of FLASH RT derives from the very short time of dose administration, which eliminates effects of organ or tumor physiological motions,[6] furthermore allowing dose escalation.

Experimental models have described an increased normal tissue tolerance to FLASH RT. Favaudon et al. (2014) studied the toxicity induced by RT to the lung of mice, observing the occurrence of severe pneumonitis and fibrosis in 100% of mice irradiated with 17 Gy at conventional dose rates; whereas no pneumonitis nor fibrosis were found after similar doses given by FLASH RT. They also noted that dose escalation up to 30 Gy with FLASH RT was necessary to induce the same degree pneumonitis and fibrosis given by 17 Gy at conventional dose rates.[7]

Other studies of the brain as a model of radiation-induced toxicity and neurocognition in mice, as a functional outcome, showed that a dose of 10 Gy given by FLASH RT, delivered at a mean dose rate above 100 Gy/s, did not alter their neurocognitive function. Cognitive sparing was demonstrated when single doses of 10 Gy were delivered at dose rates exceeding 100 Gy/s, with an apparent threshold when dose rates fell below 30 Gy/s.[8]

These experiments were the first to show that FLASH RT prevented acute and delayed complications, and therefore could also enable dose escalation. FLASH effect is observed only under physiological oxygen tension. Adrian et al. (2019)[9] irradiated prostate cancer cells at different oxygen concentrations (relative partial pressure ranging between 1.6% and 20%) with a 10 MeV electron beam at a dose rate of either 600 Gy/s (FLASH RT) or 0,23 Gy/s (conventional dose rate). Under normotoxic conditions, no differences between FLASH and conventional dose rate RT irradiation were found. For hypoxic cells (relative partial oxygen pressure of 1.6%), the radiation response was similar up to a dose of about 5-10 Gy, above which increased survival was shown for FLASH compared to conventional dose rate RT irradiation.

The increased survival was shown to be significant at 18 Gy, and the effect was shown to depend on oxygen concentration.[9] This is an important factor that should be taken in account in the decision of witch dose fraction schema will be used for treatment, as the FLASH effect seems to be present only for ablative doses.

FLASH RT causes a rapid consumption of local oxygen, faster than any tissue re-oxygenation kinetics, so reducing the radio-resistance of some tumors. This rapid depletion of oxygen would therefore elicit a transient radiation induced hypoxia, mitigating the RT damage recovery. On the other hand, the modulation of oxygen conditions by supplementation might abolish the FLASH effect, whereas depletion may have little or no additional impact.[10] In fact, there is no data that actually documents radiochemical oxygen consumption and no explanation has been provided why tumors would not be better-protected by such a mechanism.

FLASH RT also leads to instantaneous production of free radicals. The inherent differences in redox (oxidation-reduction) reactions and free radical liberation distinguish normal tissue from tumor tissue. For a given isodose, a given pulse of FLASH RT deposits significantly more energy and liberates significantly more electrons, which results in more ionization events than from conventional dose rate RT.[11] The total number of ionizations for a given dose will be the same between FLASH and conventional irradiations. It is just that the number per pulse will be higher in FLASH RT.

The observations cited above are based on FLASH RT administered in a single fraction.

Currently experiments are underway to investigate the potential benefit of FLASH RT on other tumor models using hypofractionated regimens delivered 24h apart. These models are designed to mimetize clinical RT scenarios.

Current FLASH papers have only used electrons and these cannot be considered pre-clinical. Bourhis et al. (2019)[12] published the first paper based on clinical use of FLASH RT: a 75-year-old patient with a multiresistant CD30+T-cell cutaneous lymphoma disseminated throughout the whole skin surface who had previous localized skin RT courses with poor tolerance of these RT. He was treated with FLASH RT. The treatment was given to a 3.5cm diameter skin tumor with a 5.6 MeV FLASH RT. The prescribed dose to the PTV was 15 Gy, in 90 ms. As a result at 3 weeks it was observed grade 1 epithelitis along with a transient grade 1 edema. No decrease of the thickness of the epidermis and no disruption at the basal membrane was observed, with only limited increase of the vascularization. In parallel, the tumor response was rapid, complete, and durable with a short follow-up of 5 months.

It is important to note that FLASH uses not only very high dose rates, but also high single doses, but no fractionation data have been published to date. Indeed, dose response data is extremely limited, and in some cases may reflect quite small changes in absolute dose.

CONCLUSION

The quality of life remains an unmet medical need, and points to the urgency of developing improved RT modalities for combating the cancers refractory to treatment. FLASH RT seems to prevent acute and delayed complications, allow higher doses to be given, thereby enabling dose escalation. The biological mechanisms of FLASH RT also include redox biology, which lead to tumor and NT environment modification, which may enhance RT efficacy.

DECLARATIONS

Ethics approval and consent to participate:

This manuscript does not report studies involving human participants, human data or human tissue.

Consent for publication

This manuscript does not report studies involving human participants, human data or human tissue.

Availability of data and materials

Data supporting the results reported in this article can be found and accessed by the internet. Site suggested: PubMed.

Competing interests

The author declare that he has have no competing interests.

Funding

There was no source of funding for the research.

AUTHORS' CONTRIBUTIONS

The author, himself, was responsible for the design, acquisition, analysis and interpretation of data.

ACKNOWLEDGEMENTS

Nothing and nobody to acknowledge

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