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FLASH: FLASH Leverages A Sudden Hypoxia

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Introduction

FLASH radiation therapy is a modality that uses ultra–high dose rates to achieve an increase in therapeutic window by having a reduced biological effect on normal tissue while keeping a constant effect on tumor tissue. This has been supported by different groups. Up until now the specific mechanisms at the root of this effect were unknown, although that many groups pointed towards the possibility of an oxygen depletion effect. Our group has built a planning system able to quantify the impact of this mechanism. In this paper we show a number of results applying our system to cell based experiments, pre–clinical experiments, and illustrates the effect on using modalities where the oxygenation effect is diminished (i.e. Carbon therapy)

Methods

We devised a quantification of the oxygenation effect on DNA–damage based on the oxygen fixation mechanism that is in competition with chemical repair This relationship is then used in a model describing the dose dependent oxygen depletion within a ultra-high dose pulse. The model depends on the pulse geometry: pulse length instantaneous dose rate (i.e. Gy/ns), total dose delivered in a single pulse, and initial oxygen level in a voxel. We hypothesize that the FLASH effect occurs due to the environment reaching full hypoxic conditions and therefore a reduced generation of DNA–damage.

Key results

It is clear that the initial oxygen level as well as the dose delivered provide important parameters for size (if any) of the FLASH effect Fig. 1, illustrates this by showing a relative quantification of the FLASH effect for two different intial oxygen levels as a function of the delivered dose.

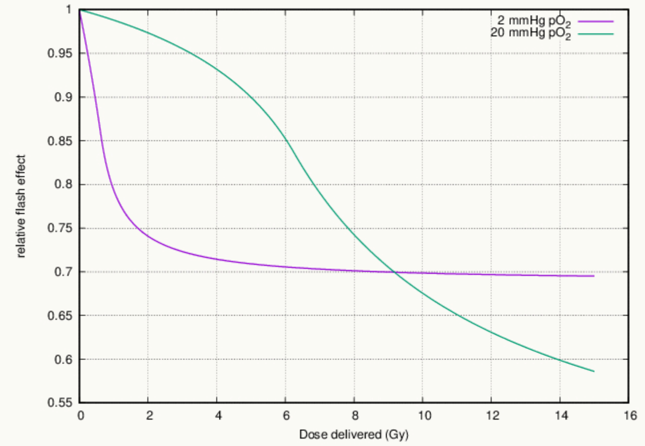

Figure 1: Relative sparing of tissue calculated with the model as a function of delivered dose. This at two different oxygen levels. The delivery used a 3.5μm long single pulse. The figure illustrates that it is needed to deliver a relatively high dose (6Gy) to exhibit a differentiation between well oxygenated and somewhat hypoxic tissue.

Here we present data from two quite different instances Fig.2a is the result from a brain treatment of mice where cognitive performance was measure as a function of dose rate. in Fig. 2b a 4D image is provided showing the changes of FLASH–effect as a function total dose, partial oxygen pressure and kinetic energy of carbon ions.

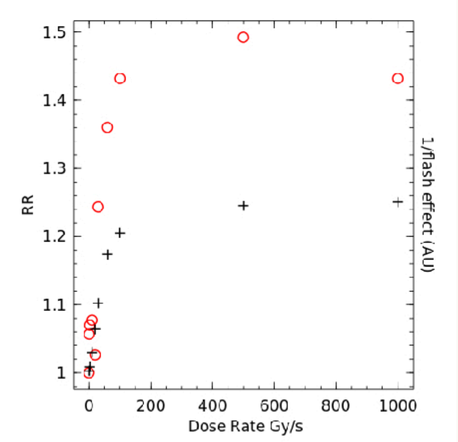

Figure 2: Left: A reconstruction of a FLASH–experiment where mice brains are subject to 10Gy radiation using a range of dose rates. Recognition rates are read out on the left, while a quantification of the FLASH effect is on the right. Our model nicely correlates with the result of this study, showing better performance in the mice as the FLASH sparing is maximal.

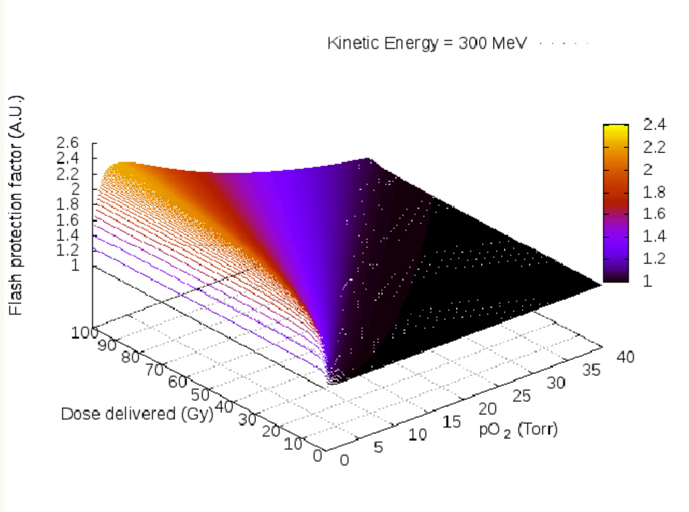

Figure 3: Applying our model to a Carbon–ion beam showing that the effect depends on the dose rate, delivered dose (per pulse) and the energy of the beam. The fixed image is provided at relatively high energies. At lower energies which can be reviewed by the reader using the controls (Acrobat Reader is needed) the FLASH effect diminishes as the Oxygen Enhancement Ratio for is diminished in a high LET regimen.

Conclusions

We have shown that a model for FLASH can be implemented based on oxygenation levels, pulse geometry, and total dose delivered can provide meaningful results.

1. The FLASH effect does not occur beneath a threshold dose (6Gy for normal tissue).
2. The FLASH effect depends on the relative LET of a particle field.
3. The FLASH effect depends on the initial Oxygen levels in the irradiated tissue.

Acknowledgements

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