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Radiation therapy and FLASH

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Cancer is a critical societal issue. Worldwide, in 2018 alone, 18.1 million cases were diagnosed, 9.6 million people died, and 43.8 million people were living with cancer. Radiation therapy (RT) is a fundamental component of effective cancer treatment and control. It is estimated that about half of all cancer patients would benefit from radiotherapy for treatment of localised disease, local control, and palliation.

The most frequently used modality of RT uses high-energy (6 to 10 MeV) photons. However, conventional photon RT is characterised by almost exponential attenuation and absorption, and consequently delivers the maximum energy near the beam entrance but continues to deposit significant energy at distances beyond the cancer target. RT has progressed rapidly with the development of new technologies and innovation leading to remarkable improvements in every phase of RT, related to treatment - from simulation to planning to delivery (image guided beams), with the aim to tailor treatment to the specific anatomy of individual patients given as result a high-precision RT.
Hadron Therapy (HT) is a precise form of RT that uses charged particles (protons and other light ions) instead of photons to deliver a dose. RT with hadrons offers several advantages since it can overcome the limitations of photons as hadrons deposit most of their energy at the end of their range (Bragg peak) and these beams can be shaped with great precision. This allows for more accurate tumour treatment, destroying the cancer cells more precisely with less damage to surrounding tissues. However, despite the recent progress of HT, numerous challenges are yet to be addressed to maximize clinical outcomes and cost-effectiveness of this advanced therapy modality to make it: (a) applicable for treating larger number of tumours, (b) accessible for a greater number of patients globally.

A simple way to boost radiation therapy efficacy is to escalate the dose to the tumour without causing normal tissue injury. Optimization of this so-called differential effect remains the holy grail of radiation therapy; a goal that may soon be reached with extreme spatial and/or temporal irradiation protocols, such as ultra-high dose rate so called FLASH-Radiotherapy where the relevant dose is delivered in fractions of a second.

FLASH-RT is causing tremendous excitement in the radio-oncology field as it may revolutionize modern day RT. Supported by radiobiological studies, FLASH-RT is a paradigm-shifting method for delivering doses within an extremely short irradiation time (tenths of a second) and Ultra High Dose in the pulse. FLASH-RT has been shown to preserve normal tissue in various species (mice, pig, cat, zebrafish) and various organs (brain, lung, gut, skin, hematopoietic system) while still maintaining anti-tumour efficacy equivalent to conventional RT at the same dose level when delivered in a single fraction or hypo-fractionated. This effect has been called the "FLASH effect"and involves in part, a decreased production of toxic reactive oxygen species.

Recent developments offer the possibility of reaching Ultra High Doses with proton-PBS, proton broad-beam as well as very high energy electron (VHEE). While, FLASH-RT has shown impressive normal tissue sparing and remarkable tumour control in *in vivo* experiments, the benefit of Proton-FLASH and VHEE-FLASH must be confirmed.

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