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# Validation of Trento's Proton Centre for FLASH Radiotherapy: A Comparative Analysis, Insight from Zebrafish

Radiotherapy is one of the main treatment options for cancer patients. The delivery of radiation sources and the reduction in damage to the surrounding healthy tissues have made significant progress in recent years. Particularly, the emergence of Ultra High Dose Rate (UHDR, also known as FLASH) radiotherapy is encouraging because it enhances treatment efficacy while minimizing side effects. Unlike conventional radiation therapy, which irradiates the target for an extended period, FLASH radiotherapy delivers radiation in ultra-high doses per fraction, potentially sparing the surrounding normal tissues while maintaining tumor control.
In addition, irradiating in conditions with reduced oxygen concentration (hypoxia) may confer advantages by exploiting the differential response of tumor cells to radiation. Hypoxia, a common feature of solid tumors, has been associated with increased radioresistance and reduced efficacy of conventional radiotherapy. However, the FLASH regime may overcome the radioresistance associated with hypoxia, resulting in improved tumor control and reduced normal tissue toxicity.
In this study, we conducted a comparative analysis with what was recently obtained by a research group based in Dresden to examine similarities and disparities in irradiation outcomes. Experiments were performed on 1 day post fertilization zebrafish embryos. To evaluate the impact of oxygen concentration on irradiation efficiency (both conventional and UHDR) and healthy tissue sparing effect, zebrafish embryos were irradiated in normoxia or hypoxia (2.5% O2). To do so, approximately 2 hours before irradiation, about 30 embryos for each experimental condition were placed in 0.5 ml Eppendorf tubes filled with 200 µl low melting agarose and around 300 µl E3 embryo medium. Hypoxia was applied by placing the embryos within the InViVO2 hypoxic chamber (Ruskin) for 90 minutes in order to reach the desired Oxygen concentration (measured using the Presens Oxygen sensor). After this incubation, Eppendorf tubes with the embryos were sealed and moved to the Trento Proton Therapy Centre for irradiation. Both normoxic and hypoxic zebrafish embryos were irradiated with conventional and UHDR proton beam with a total radiation dose of 30 Gy. After irradiation, the embryos were moved to 96-well plates and maintained under normal conditions (28 °C) with medium exchange every other day. We acquired images daily until 120hpf by analyzing five biological endpoints (pericardial edema, curved spine, head diameter, embryo length, and eye diameter). All malformations were scored and normalized with the controls.
Preliminary results suggest that the FLASH regime may have a potential protective role towards damages, particularly on spinal damage.
Taken together, these preliminary results confirm that irradiation in hypoxic conditions appears to play a protective role on healthy tissues, particularly evident when combined with the FLASH regime.

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