Radiobiology and Imaging Program (RBI) Retreat 2025

Chronic Radiation Toxicities Are Attenuated Following Fractionated Proton FLASH Radiotherapy

Anastasia Velalopoulou[1], Ilias V. Karagounis[2], Michele Kim[1], Seyyedeh Azar Oliaei Motlagh[1], Eric Diffenderfer[1], Amit Maity[2], Costas Koumenis[1], Keith Cengel[1], Theresa Busch[1]

1. Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania
2. Department of Radiation Oncology, Huntsman Cancer Institute, University of Utah

Abstract

***Background*:** Preclinical data suggest that proton FLASH radiotherapy (F-PRT) offers a promising strategy to enhance the therapeutic ratio by reducing normal tissue toxicity while preserving tumor control. Studies have demonstrated comparable tumor control dose (TCD_{50}) values between FLASH and conventional proton therapy, indicating equivalent antitumor efficacy [1]. Notably, single dose FLASH radiotherapy has been associated with reduced skin toxicity and fibrosis, suggesting a favorable dose-modifying effect (DME) [2].
***Aim*:** This study aimed to quantify the dose-modifying factor (DMF) using fractionated FLASH proton regimens and evaluate long-term normal tissue outcomes to further define the therapeutic potential of FLASH for clinical translation.
***Methods*:** All animal experiments adhered to IACUC protocols at the University of Pennsylvania. A 230 MeV proton beam from an IBA Proteus Plus C230 Cyclotron was used to irradiate the right hind leg of C57BL/6J mice with 3 fractions of 10, 12.5, 15, 17, or 25 Gy administered every 48 hours. A double-scattered system ensured a uniform 2 × 2 cm^2 field. Proton beams were delivered as shoot-through transmission using either FLASH (69-124 Gy/s) or standard (0.39-0.65 Gy/s) dose rates. DMF was calculated based on the incidence of radiation-induced dermatitis, lymphedema and fibrosis, over a 3-month period. Nonlinear regression was used to estimate median doses inducing severe toxicity in 50% of mice (SDD_{50}, SLD_{50} and SFD_{50}).
Results: Fractionated F-PRT significantly mitigated normal tissue toxicity across multiple endpoints. The severe dermatitis dose in 50% of mice (SDD_{50}) was 12.86 Gy for S-PRT (95% CI: 7.03-18.15) and 13.84 Gy for F-PRT (95% CI: 13.22-14.45), corresponding to a DMF of 1.07. For lymphedema, the severe threshold dose (SLD_{50}) increased from 14.13 Gy with S-PRT to 17.87 Gy yielding a DMF of 1.26 and indicating substantial lymphatic tissue sparing. Similarly, the dose required to induce severe fibrosis (SFD_{50}) was 13.86 Gy for S-PRT (95% CI: 12.35-15.78) and 17.58 Gy for F-PRT (95% CI: 15.40-65.41), resulting in a DMF of 1.27. These findings underscore the enhanced protective effect of F-PRT, particularly for chronic toxicities such as lymphedema and fibrosis.
Conclusions: Fractionated proton FLASH radiotherapy demonstrated a clear dose-modifying effect, reducing both skin and lymphatic toxicity. The more pronounced protection observed for fibrosis supports the continued investigation of F-PRT for clinical applications aimed at minimizing late normal tissue complications.