

Abstract title: Flash proton re-irradiation with hypofractionation mitigates radiation-induced toxicity of the head and neck tissues in mice

Priyanka Chowdhury¹, Michele M. Kim¹, Yuewei Lin², Ling Qin², James Metz¹, Alexander Lin¹ and Constantinos Koumenis^{1*}

¹ Department of Radiation Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

² Department of Orthopedic Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA

The effect of FLASH Proton Radiation therapy (F-PRT) in decreasing normal tissue toxicity while maintaining equal tumor control compared to Standard Proton Radiation therapy (S-PRT) has been previously investigated for head and neck tissues in mice using a single dose of either S-PRT/F-PRT. Here, we studied the effect of F-PRT in a re-irradiation setting with hypofractionation.

The head and neck area of C57Bl/6 mice was irradiated with two different re-irradiation schemes. In one scheme, mice were irradiated with a single dose of 12 Gy of S-PRT (0.95 Gy/s) and after four weeks, those mice were re-irradiated with a hypo-fractionated dose of 6 Gy x 3 of either S-PRT or F-PRT (128Gy/s). In another scheme, the dose was escalated, and the mice were first irradiated with a single dose of 14 Gy of S-PRT, followed by a hypo-fractionated dose of 9 Gy x 3. Radiation-induced xerostomia was studied by measuring the saliva flow rate of mice. Mice were also examined for the histopathological changes.

Compared to the re-irradiation with S-PRT, F-PRT re-irradiated mice mitigates xerostomia by improving salivary flow as observed with both the re-irradiation schemes. Histopathological analysis of the salivary gland showed increased acinar cell atrophy and individual cell death in the submandibular gland in mice re-irradiated with S-PRT compared to those with F-PRT. Re-irradiation with hypo-fractionated S-PRT showed a significant increase in the alveolar bone loss compared to F-PRT. Submucosal fibrosis, as assessed by Masson's trichrome staining of the irradiated tongues, was significantly increased at day 45 post- re-irradiation with S-PRT compared to the ones re-irradiated with F-PRT.

This study provides evidence of the sparing effect of F-PRT in minimizing radiation-induced head and neck tissue toxicity in a hypo-fractionated re-irradiation setting. The results support the efficacy of F-PRT for clinical application.