Proton FLASH Radiotherapy: From preclinical studies in mice and canines to human clinical trials.

Despite technological advances in conformal delivery of Radiation Therapy (RT), there is still incidental dose deposition to normal tissues resulting in significant toxicities and morbidity, thereby limiting the efficacy of some RT modalities. About a decade ago, landmark animal studies using ultra-high dose rate ("FLASH") RT, generated tremendous excitement due to this modality's reduced normal tissue toxicity and equipotency with conventional RT in controlling tumor growth. Since then, numerous studies have demonstrated similar results in multiple mouse models and larger animals. Remarkably, a safety-feasibility clinical trial with proton FLASH RT in patients with metastatic bone cancer has been completed and others are ongoing or being planned. The mechanisms behind the sparing effects of FLASH are still obscure and actively being investigated. In this talk, I will present recently published and unpublished results from our group and collaborators, under a multi-institutional, NIH-funded P01 project on particle FLASH therapy. Using mouse and canine normal and tumor tissues from GI, Bone and Head and Neck organs, we found strong evidence supporting reduced toxicity of normal tissue following proton FLASH compared to Standard RT but no tumor radioprotection. I will present data, which support a model of stem/progenitor cell sparing by Proton FLASH RT discuss potential molecular mechanisms behind this effect. Finally, I will present data form a completed trial in canines with Head and Neck Cancer treated with Conformal proton FLASH and preliminary work towards a human patient trial in H&N cancer.

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