

## EMERGING PARTICLE THERAPY STRATEGIES: PROTON MINIBEAM RADIATION THERAPY, ION MINIBEAM RADIATION THERAPY, AND PARTICLE FLASH RADIOTHERAPY

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Particle therapy is undergoing a major transformation driven by the development of innovative irradiation strategies aimed at increasing the therapeutic index by enhancing tumor control while minimizing normal tissue toxicity. Among the most promising approaches are Proton Minibeam Radiation Therapy (pMBRT), Ion Minibeam Radiation Therapy (iMBRT), and particle FLASH radiotherapy, all of which have demonstrated remarkable potential in preclinical studies.

Proton Minibeam Radiation Therapy employs arrays of submillimetric proton beams to create highly spatially modulated dose distributions. This approach has been shown to significantly improve normal tissue preservation while maintaining, and in some cases enhancing, tumor control. Building upon this concept, Ion Minibeam Radiation Therapy extends spatial fractionation to heavier ions, combining the favorable radiobiological properties of charged particles with the tissue-sparing benefits of minibeam irradiation. These characteristics make iMBRT particularly attractive for the treatment of radioresistant and deep-seated tumors.

In parallel, particle FLASH radiotherapy delivers therapeutic doses at ultra-high dose rates, typically exceeding 40 Gy/s, producing the so-called FLASH effect: a remarkable reduction in radiation-induced damage to normal tissues while preserving antitumor efficacy. The integration of spatially fractionated minibeam with ultra-high dose rate delivery has recently emerged as an exciting research avenue, with the potential to further enhance the therapeutic window of particle therapy.

This lecture will provide an overview of the physical, dosimetric, and radiobiological principles underlying these emerging modalities. Key preclinical findings, proposed biological mechanisms, technological challenges, and ongoing efforts toward clinical translation will be discussed. Particular attention will be given to the opportunities offered by combining spatial fractionation and ultra-high dose rate irradiation, highlighting how these strategies may contribute to the next generation of precision radiotherapy treatments.