PROJECT

Supervisor: Antonello Enrico Spinelli

Title: Preclinical Minibeam Radiotherapy: Mechanisms and Therapeutic Potential

Curriculum: Cell and Molecular Biology

Link to the personal page of the University or relevant hospital site website: https://research.hsr.it/en/core-facilities/preclinical-imaging/antonello-spinelli.html

Description of the Project (max 3,000 characters including spaces)

Background/gap of knowledge

Radiotherapy (RT), an essential tool for cancer treatment, aims to deliver a curative dose to the tumor precisely while sparing surrounding healthy organs. Although healthy tissue doses have been dramatically reduced thanks to sophisticated beam delivery methods combined with accurate image-guidance systems, treatment-related adverse effects are still among the major limiting factors of RT efficacy. Novel preclinical approaches have been developed to tackle problems like these, such as mini-beam radiotherapy (MBRT)[1-5]. MBRT is based on hight dose gradient regular beam pattern resulting in non-uniform dose profiles of high and low-dose regions defined as peak and valley, respectively

Rationale and hypothesis

Classical radiobiology concepts fail to explain MBRT and immunomodulatory effects are likely to be a key factor among the proposed mechanisms. MBRT has been shown to enhance immune activity by improving the accessibility of effector immune cells to the tumor, either by activating specific inflammatory pathways or by modulating the extracellular matrix [1]. Additionally, MBRT increases monocyte infiltration into tumors, which is essential for secreting type 1 interferon in the tumor microenvironment. This process enhances the RT-induced CD8+ T-cell antitumor response[5], which is closely linked to the effectiveness of immune checkpoint inhibitors and RT combinations in GMB. The immunomodulatory effects of MBRT provide a strong rationale for exploring MBRT in combination with immunotherapy (MBRT-IT).

Objectives and specific aims

1 Evaluate the tumor and healthy tissue response using different radiation doses and mini-beam dimensions.

With this aim, we plan to investigate the effects on tumors and normal tissue (skin) of different radiation beams and valley dimensions. The mini-beam treatments will be carried out using different collimators. In particular the main features of the mini-beam collimators that will be investigated in this proposal are beam width, center-to-center distance, thickness, material, and geometry. These parameters will allow us to obtain collimators producing different spatial dose patterns and peak-to-valley dose ratios.

2 Investigate the role of radiation-induced cohort effects linked to tumor microenvironment modification after mini-beam radiotherapy.

As described above, one of the keys of MBRT is the sparing of normal tissue while maintaining at the same time local tumor control. In this proposal, we plan to improve the efficacy of RT against GBM tumors by studying the immune mechanisms relying on the activation of cytokines and immune cells. Glioma-associated macrophages/microglia (GAMs) play a critical role in GBM progression due to their extensive recruitment to the tumor site and their polarization into a tumor-promoting phenotype.

Expected outcomes

Combining immunotherapy with strategies like MBRT, which counteract immunosuppressive mechanisms, could enhance immune responses and improve treatment outcomes. To explore this potential, we will investigate MBRT versus CONV RT in combination with anti-CTLA-4 monoclonal antibodies using an immunocompetent murine glioma model.

Skills that the student should acquire (max. 600 characters including spaces):

The student PhD will acquire state of the art preclinical *in vivo* minibeam radiation therapy skills, in particular radiation physics, radiobiology, and animal experimentation. Key areas include dosimetry, beam delivery, imaging, and tumor models, along with ex vivo analysis.

References (max. 15)

[1] C. Fernandez-Palomo et al., "Animal models in microbeam radiation therapy: A scoping review," 2020. doi: 10.3390/cancers12030527.

[2] S. Francesca Marson, "Real-time dose measurement in minibeam radiotherapy using radioluminescence imaging ," Physica Medica, Jan. 2025.

[3] A. Bertho et al., "Evaluation of the Role of the Immune System Response After Minibeam Radiation Therapy," Int J Radiat Oncol Biol Phys, vol. 115, no. 2, 2023, doi: 10.1016/j.ijrobp.2022.08.011.

[4] C. Koksal Akbas et al., “Preclinical photon minibeam radiotherapy using a custom collimator: Dosimetry characterization and preliminary in-vivo results on a glioma model,” Physica Medica, Jul. 2024, doi: https://doi.org/10.1016/j.ejmp.2024.103420.

[5] Pizzardi S, Alborghetti L, Vurro F, Lacavalla MA, Capialbi MM, Milani P, Cavaliere F, Fiorino C, Spinelli AE. Development of a preclinical X-rays minibeam Monte Carlo treatment planning system. Sci Rep. 2025 Aug 15;15(1):29926. doi: 10.1038/s41598-025-15281-5. PMID: 40817138; PMCID: PMC12356841.

[6] S. Tadepalli et al., “Rapid recruitment and IFN-I-mediated activation of monocytes dictate focal radiotherapy efficacy,” Sci Immunol, vol. 8, no. 84, 2023, doi: 10.1126/SCIIMMUNOL.ADD7446.