Immune and Bystander/Abscopal Effects of Spatially Fractionated GRID and Lattice Radiation Therapy

Seema Gupta 1, Xiaodong Wu 2, Samir Khleif 3, Mansoor Ahmed 4

1. Lombardi Cancer Center, Georgetown University Medical Center, Washington, USA 2. Radiation Oncology, Innovative Cancer Institute, Cyberknife Center of Miami, South Miami, USA 3. Cancer Center, Georgia Regents University Cancer Center, Augusta, USA 4. Radiation Research Program, National Cancer Institute, Rockville, USA

Corresponding author: Seema Gupta, sg1335@georgetown.edu

Categories: Medical Physics, Radiation Oncology
Keywords: grid, spatially fractionated radiation therapy (grid)

How to cite this abstract

Abstract

OBJECTIVES: To evaluate the effects of high-dose 2-dimensional spatially-fractionated GRID radiation therapy (SFGRT) and a dosimetrically superior 3-dimensional lattice RT (LRT) on local and metastatic/distant tumor control and the role of radiation-induced bystander/abscopal effects and immunomodulation in xenograft and syngeneic mice tumor-models.

METHODS: Contra-lateral tumors were developed in right (RT) and left (LT) flanks of the nude (A549 lung adenocarcinoma) or C57BL/6 (Lewis lung carcinoma 1; LLC1) mice that were subjected to SFGRT (Xenografts): high-dose SFGRT (15Gy)/conventional ionizing-radiation (CIR; 7.5Gy) to LT with/without additional CIR-fractions (2Gy for 5 days) to RT/LT; and LRT (syngeneic-tumors): two 10% of tumor-volume vertices, one 20% vertex, one 50% vertex and 100% open-field IR (single-dose of 20Gy to LT). Tumor growth, effects on negative regulators of ceramide, apoptosis as well as immune responses were determined.

RESULTS: In nude-mice-xenograft model following SFGRT: 1) Both irradiated and un-irradiated tumors in each individual-mouse responded strikingly similar to the treatment. 2) The radiation-induced bystander/abscopal effects were additive, leading to more robust effect with high-dose radiation followed by CIR-fractions. 3) Maximum abscopal effect was observed after SFGRT+CIR-fractions to the same tumor. 4) Time-reversal characteristic of the abscopal effect was demonstrated for the first time. Increase in Bax/Bcl-2 ratio, sphingosine-kinase, and expression of TRAIL and TNF was observed following SFGRT and SFGRT+CIR-fractions in LT.

In syngeneic-tumors following LRT: 100% open-field and 20% volume-irradiation (in two 10% volumes) resulted in significant growth delay in the irradiated tumor. Both partial or 100% volume-irradiation demonstrated distal effectiveness. Mice treated with partial tumor-volume radiation showed increased CD3+ cells, TRAIL, IFN-gamma and Th1 response and down-modulated Th2 functions compared to whole-tumor irradiation. Further, serum obtained from LRT-treated mice caused enhanced growth-inhibition of endothelial cells compared to untreated or open-field IR groups.

CONCLUSIONS: These results demonstrate that spatially-fractionated or partial-volume high-
dose hypofractionated RT is therapeutically more effective than conventional whole-tumor volume RT and causes an improved distant effect. Importantly, significant bystander/abscopal effects observed in the nude mice-model suggest that anti-tumor effects of high-dose hypofractionated radiation are mediated not only through activation of host immune-system but also by modulating other pathways regulating cancer progression and metastasis.