

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

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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 and RT.

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-

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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.