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Threshold Dose in Spatially Fractionated Radiation Therapy for Preclinical Triple-Negative Breast Cancer

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Abstract

Objectives:

Clinical studies of spatially fractionated radiation therapy (SFRT) followed by conventional radiotherapy have shown promising results for treating bulky tumors. However, the specific dosimetric parameters of SFRT that are critical for optimizing tumor control and reducing toxicity remain unclear. This study aimed to evaluate the contributions of peak dose, valley dose, and equivalent uniform dose (EUD) in a preclinical syngeneic murine model of triple-negative breast cancer.

Methods:

4T1 murine carcinoma cells were injected subcutaneously into the bilateral hindlimbs of adult BALB/c mice. Tumors measuring 5–10 mm in diameter were irradiated using either whole-tumor radiation or GRID collimators. The GRID collimators consisted of brass plates (3 mm and 5 mm thick) with three equally spaced, 3 mm-diameter holes. The holes were separated by 2 mm, resulting in a center-to-center distance of 5 mm. Irradiation was performed using an XRD-320 small animal irradiator at 250 kV, 16 mA, and 50 FSD, with a field size of 10 x 10 cm. The remainder of the mouse was shielded with a lead shield. Mice were randomized into groups of three, and ipsilateral hindlimb tumors were irradiated using a 3-hole GRID collimator with a thickness of 3 mm (peak-to-valley dose ratio (PVDR) of 3), a 5 mm-thick GRID collimator (PVDR of 7), or a whole-tumor open field at escalating doses of 10 Gy, 15 Gy, 20 Gy, 22 Gy, and 25 Gy. A control group remained unirradiated, and contralateral tumors were not treated. Tumor growth and survival were monitored.

Results:

Doses of 10, 15, and 20 Gy resulted in greater tumor volume reduction in both irradiated and untreated tumors in mice treated with open-field radiation compared to those treated with either GRID collimator. At 22 and 25 Gy, similar decreases in tumor volume were observed in both irradiated and untreated tumors for mice in the open-field and GRID-treated groups. There were no significant differences in median survival times between the groups.

Conclusion(s):

This study is hypothesis-generating, suggesting that a threshold peak dose may be required to trigger immune effects from SFRT in a preclinical syngeneic murine model of triple-negative breast cancer. The results were similar between the mouse cohorts with different PVDRs, and therefore different valley doses. Both the whole-tumor treated and GRID-treated mice exhibited comparable abscopal effects in the contralateral untreated tumors at 22 Gy and 25 Gy. Survival rates were also similar between the GRID-treated and whole-tumor treated groups, indicating that both cytotoxicity and immune responses may have contributed to overall survival in the GRID-treated mice.