

Microbeam Radiation Therapy of Human Glioblastoma Multiforme in Nude Mice

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Beamline(s): X17B1

Introduction: About 40% of all primary brain tumors are high grade astrocytomas, which are extremely refractory to regular therapies such as surgery, chemotherapy and conventional radiation therapy. Patients with glioblastoma multiforme (GBM), which is a high grade astrocytoma, have a median survival time of approximately 8-10 months. Microbeam radiation therapy (MRT), which utilizes arrays of parallel, synchrotron-generated, thin planar slices of x-ray beams, has been demonstrated to spare normal tissues such as brain, spinal cord, and skin in laboratory animals in single-fraction irradiations. At the same time, single-fraction MRT ablates or palliates tumors such as the rat intracranial 9L gliosarcoma (9LGS) in unidirectional and bi-directional treatments. In the present study unidirectional microbeams generated at the X17B1 beamline were used to evaluate the therapeutic efficacy of MRT against a human GBM xenograft in mice.

Methods and Materials: Athymic NCr/Sed nude mice were implanted with human GBM U87. Small chunks (1-1.5 mm) of source U87 tumors were transplanted subcutaneously into the calf area of the right hindleg of animals. After the size of tumors reached about 6 mm in diameter, they were irradiated with an array of vertical microbeams, each 90 μm wide, with 300 μm center-to-center spacing (labeled 90/300 μm beam below). The single-fraction, in-slice skin-entrance doses were the following: Group A (n=6) 950 Gy microbeams; Group B (n=6) 700 Gy microbeams; and Group C (n=6) unirradiated controls. Tumor response to radiation was quantified using the parameter Tumor Growth Delay, defined as the difference in days between the median time required for tumors in the treated and the control animals to reach a volume three times that measured on the day of treatment. The width of the irradiated area was 30 mm.

Results: The doses used were below the skin damage threshold except for minor hair loss. The irradiations delayed the tumor growth significantly. The Growth Delay was 42.5 days and 38 days in the 950-Gy and 700-Gy dose groups, respectively. Wilcoxon rank order test indicated a statistically significant difference for microbeam groups versus unirradiated controls ($p < 0.01$). Monte Carlo simulations showed that the radiation leakage dose between the microbeams (i.e. the "valley dose") was about 1.5% of the peak dose.

Conclusions: The results obtained demonstrate a substantial response of the highly radioresistant human GBM U87 in nude mice to 90/300 μm microbeams. This effect cannot be solely explained by direct radiation killing of tumor cells because about 70 % of tumor volume was only subjected to the valley irradiation at a low dose of 10-14 Gy. Studies with higher dosage microbeams are planned; our other MRT studies indicate that mouse skin can tolerate microbeams doses 60% more than the highest dose used in this study.

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