#4712. Image-Guided Focal Irradiation in Syngeneic Preclinical Oncology Mouse Models

Sarah Krueger, Thomas Dailey, Kevin Guley and Maryland Rosenfeld Franklin
Labcorp Early Development Laboratories Inc., Ann Arbor, Michigan

Introduction and Background

- Use of image-guided focal irradiation is a mainstay of human cancer treatment.
- Image guidance allows for highly conformal treatment plans that minimize normal tissue toxicity and systemic response.
- With the advent of image-guided small animal irradiators such as the Small Animal Radiation Research Platform (SARRP; Xstrahl Inc., Suwanee, GA), targeted focal irradiation can now be utilized in a broad range of preclinical oncology models.
- Of particular interest is the possible use of focal irradiation to broaden the efficacy and response duration of immuno-oncology therapy.

Materials and Methods

- Image-guided irradiation was performed under 1-2% isoflurane anesthesia on the Small Animal Radiation Research Platform (SARRP; Xstrahl Inc., Suwanee, GA). Following placement on the treatment bed, animals were imaged with an open field at 60 kV and 0.5 mA for a planning CBCT. The resultant CT was then loaded into the treatment planning software (Muriplan, Xstrahl Life Sciences) and a treatment plan applied and optimized for each target.
- Treatment was delivered at 220 kV and 13.0 mA using an appropriately sized collimator to the total indicated dose (in Gray; Gy) in 2 equally weighted beams. For daily treatments, the same treatment plan was applied and adjusted for changes in animal positioning or target alteration over time.
- Bilateral subcutaneous (SC) mouse tumor models tested were A20 (B cell lymphoma; Balb/C mice) and RIF-1 (sarcoma; C3H mice) and an intracranial (IC) GL261-luc (glioblastoma; albino C57BL/6 mice) model.
- In the SC models, focal irradiation was delivered only to the right side tumors and tumor growth changes tracked by caliper measurements for both right and left side implants. Mice were euthanized when a combined tumor volume of approximately 2,000 mm^3 was reached.
- In the GL261-luc model, mice were implanted intracranially on Day 0 with 1.00E+06 cells per 10 µL. Mice were injected with Carprofen at 5 mg/kg and anesthetized using 2% isoflurane and then secured in a stereotaxic frame (ASI Instruments, Inc.). Cells were implanted 2 mm right lateral and 1 mm anterior of the bregma. The burr hole was sealed with bone wax and the incision was closed with a stainless steal wound clip. Wound clips were removed 7-10 days post-implant.
- In the IC model, focal irradiation was delivered to the brain and tumor burden was tracked by bioluminescence imaging (BLI) over time. BLI was performed using an IVIS Spectrum (Caliper Life Sciences, Hopkinton, MA).

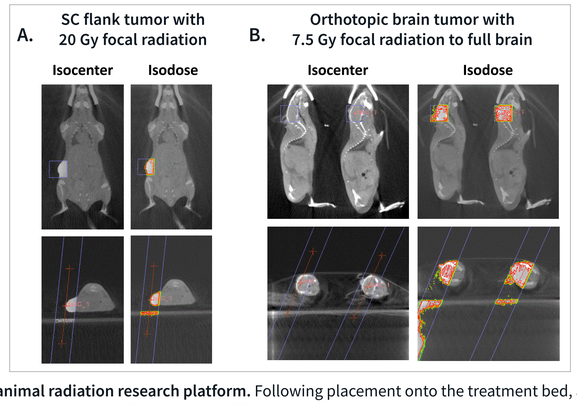

Figure 1. Small animal radiation research platform. Following placement onto the treatment bed, a CBCT is performed for treatment planning. The resultant CT is then loaded into the treatment planning software and a treatment plan is optimized for each target. In A and B, treatments were delivered using a 10x10 collimator and the total indicated dose (in Gray; Gy) was administered in 2 equally weighted beams. The isodose figures shown on the right hand panels of A and B show homogeneity of the delivered dose with limited/no scatter.

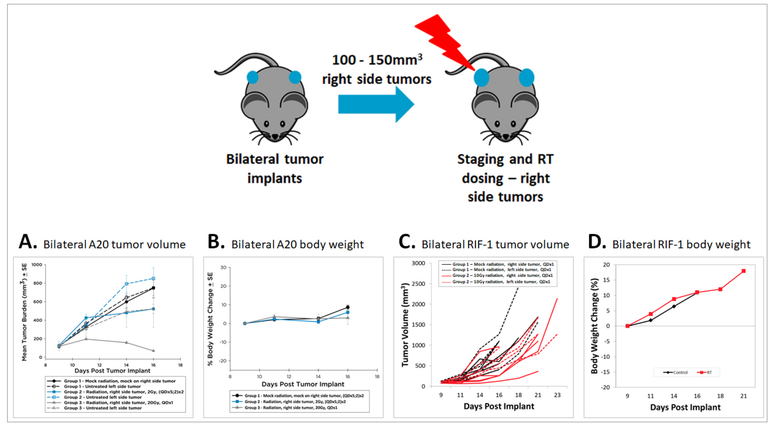

Figure 2. Sensitivity of bilateral tumor models to focal radiation. A20 (A, B) or RIF-1 (C, D) tumor cells were bilaterally implanted into the appropriate syngeneic mouse strain. When right side tumor volumes reached 100-150 mm^3 mice were sorted into treatment groups and mock or focal radiation initiated on right side tumors only. For the A20 study, mice received 2 Gy for 5 days on/2 days off for 2 cycles (A, light blue lines) or a single dose of 20 Gy (A, gray lines). For the RIF-1 study, mice received mock radiation (C, black lines) or a single dose of 10 Gy radiation (C, red lines). Tumor volumes of right side tumors (A & C, solid lines) and left side tumors (A & C, dashed lines) were monitored over time. In B & D, body weight changes were tracked over time. None of the utilized radiation treatments resulted in body weight loss. A20 is more sensitive to radiation treatment than RIF-1.

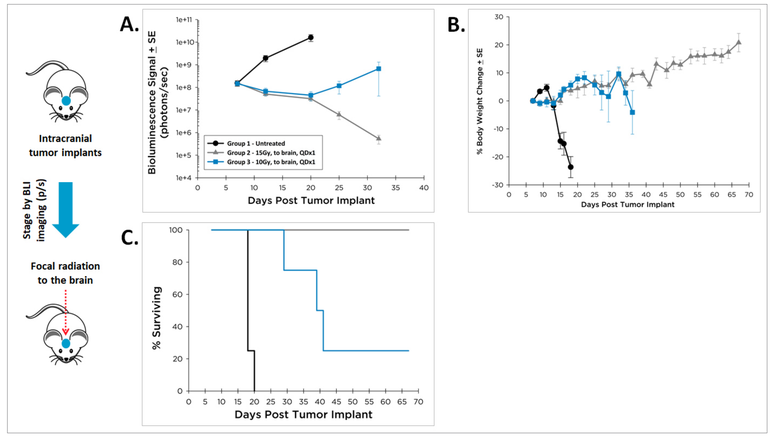

Figure 3. Sensitivity of murine GL261-luc to focal radiation. GL261-luc cells were implanted intracranially into albino C57BL/6 mice. Mice were staged into treatment groups on Day 7 based on BLI (photons/second) imaging. Mice received a single, focal dose of radiation, either 10 Gy (blue line) or 15 Gy (gray line). Tumor burden (A) and body weights (B) were monitored over time. Mice were removed from study at ~20% body weight loss. Overall survival for the treatment groups was plotted against control (C) to illustrate the increased lifespan following radiation treatment. A single dose of 10 Gy was chosen for follow on work.

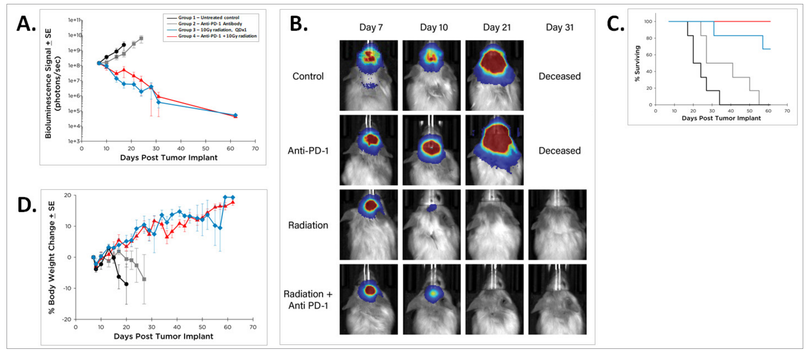

Figure 4. Anti-PD-1 antibody in combination with focal radiation in the murine GL261-luc intracranial tumor model. Mice received no treatment (black lines), 10 mg/kg anti-PD-1 antibody (gray lines), 10 Gy radiation (blue lines) or the combination (red lines). Tumor burden was tracked over time (A, B) along with overall survival (C) and body weight changes (D). Single agents increased life-span vs. control. The combination resulted in 100% survival.

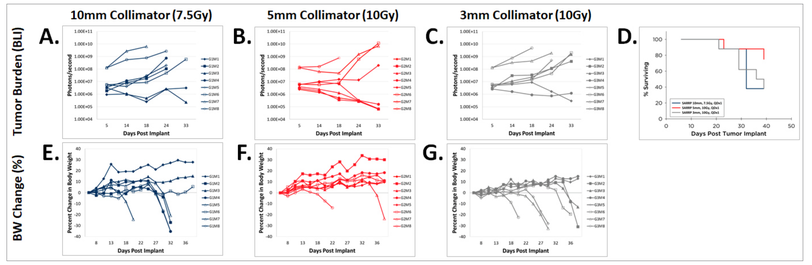

Figure 5. Optimization of focal radiation delivery to the brain in the GL261-luc intracranial tumor model. Tumor burden was monitored with in vivo BLI imaging (A, B, C). Body weight changes over time were measured (E, F, G). Overall survival was compared between groups (D).

Results and Conclusions

- The A20 and GL261-luc tumor models are more sensitive to radiation treatment than the RIF-1 tumor model.
- Bilateral tumor models can be utilized to evaluate the effects of focal radiation on both the primary tumor and the contralateral tumor. This can help assess abscopal effects of radiation therapy.
- GL261-luc is a useful model to test the effect of focal radiation in combination with immunotherapies for glioblastoma.
- Understanding the optimal radiation dose and delivery is important to ensure a meaningful study outcome.
- Future studies are being run in the GL261-luc model to understand the immune profile following radiation and/or immunotherapy treatments.
- Additional work to determine the sensitivity of other syngeneic tumor models to focal radiation is currently ongoing.

Presented at the AACR Annual Meeting 2017

©2022 Laboratory Corporation of America® Holdings All rights reserved.

labcorp Drug Development