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Abstract Category – Soft Tissue Tumors

Abstract Title: Prophylactic eFLASH Pulmonary Radiation Inhibits Lung Metastases and Improves Survival in a Murine Soft-Tissue Sarcoma Metastatic Model

Abstract

Significance / Hypothesis / Technique:

Approximately 50% of patients presenting with localized high-risk soft tissue sarcoma (STS) develop incurable metastases despite current treatment regimens including systemic therapy, wide surgical resection and radiation of the primary tumor. We previously showed prophylactic pulmonary radiotherapy with conventional photon beams decreased lung metastatic burden and prolonged survival in a proof-of-principle murine STS model. This study is a continuation of the concept, utilizing electron FLASH-RT (eFLASH) to minimize normal tissue toxicity, facilitate whole lung irradiation (WLI) and increase efficacy.

Innovation:

Administration of prophylactic pulmonary radiation in the setting of localized high-risk primary STS to prevent development of innumerable and incurable metastases arising from circulating tumor cells and pre-clinical / microscopic lung deposits is a completely novel approach in this field.

Approach:

Thirty-two immunocompromised mice received tail vein injection of HT-1080-Luc human fibrosarcoma cells. Three days post-injection, mice were randomized to four groups (n=8 each): (1) Sham control; (2) Hemithoracic irradiation (HTI) with conventional dose rate (CONV, 0.4 Gy/s); (3) HTI with eFLASH (~80 Gy/s); (4) WLI with eFLASH (~80 Gy/s). The prescribed radiation dose was 15 Gy (mean delivered doses: CONV-HTI 14.3 Gy, eFLASH-HTI 13.8 Gy, eFLASH-WLI 13.3 Gy). Tumor burden was assessed by bioluminescence imaging (BLI) Xenogen IVIS, up to three times weekly. Endpoints included survival, body weight, and histopathological analysis of lungs at necropsy

Results:

WLI eFLASH significantly prolonged median survival (33.0 days; 95% CI: 30.9–35.1) compared to sham (18.0 days), HTI-CONV (21.0 days; 95% CI: 19.7–22.3), and HTI-eFLASH (24.0 days; 95% CI: 20.4–27.6) (Log-rank $p < 0.001$). One mouse (12.5%) in the WLI-eFLASH group remained alive at study completion.

WLI eFLASH demonstrated effective tumor control in irradiated lung fields, with suppressed BLI signal maintained throughout the study for the lung fields. Mice that received WLI eFLASH succumbed to extra-pulmonary metastases such as in the liver. The non-irradiated lung fields in the control group and the HTI groups developed progressive lung metastases as well as extra-pulmonary disease which led to mortality.

Decreased TGF-β1 expression in eFLASH-treated tissues (HTI-eFLASH: 2.8; WLI-eFLASH: 3.0 vs. HTI-CONV: 4.0 in contralateral lung) suggested a reduced fibrotic potential compared to conventional radiation. WLI eFLASH treated mice maintained their body weight longer, suggesting tolerance of the greater extent of pulmonary radiation along with delayed disease progression.

Discussion / Impact:

This study provides additional support for the principle of prophylactic pulmonary radiation for localized high-risk STS to inhibit future development of incurable lung metastases and to improve survival. WLI eFLASH maintained efficacy, minimized pulmonary fibrosis and demonstrated tolerability in mice. These findings warrant further investigation leading toward potentially a clinical trial.

Figures:

Figure 1: Kaplan-Meier Survival Curve

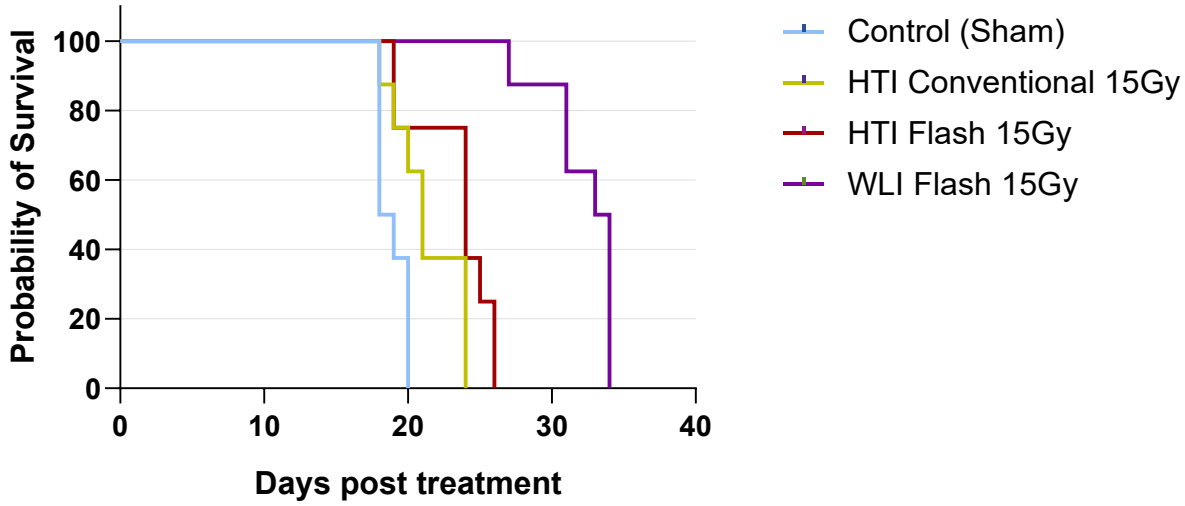
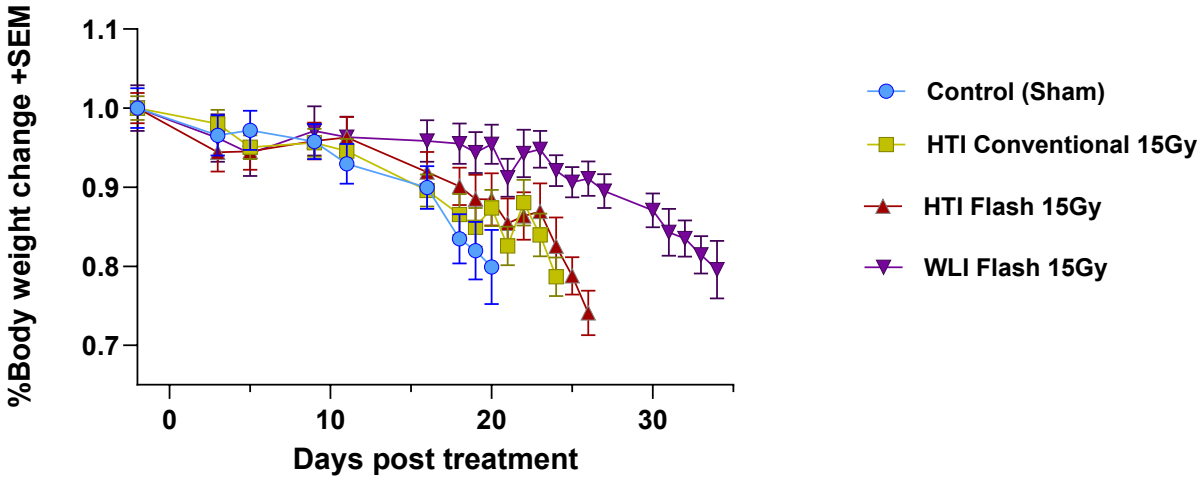


Figure 2: Body Weight vs. Time


%Body weight change +SEM
1.1
1.0
0.9
0.8
0.7
0
10
20
30
Days post treatment
Control (Sham)
HTI Conventional 15Gy
HTI Flash 15Gy
WLI Flash 15Gy