Stepping Towards Conformal Delivery: A UHDR Multiple-Beam Study

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ABSTRACT

Purpose: The goal of this project was to investigate whether the FLASH skin-sparing effect is preserved across multi-beam ultra-high-dose-rate (UHDR) deliveries and to characterize the accompanying in vivo tissue oxygen dynamics within a 5-second total treatment window previously shown to maintain sparing.

Methods: Mice were irradiated at three dose levels (23.6, 25.2, and 25.9 Gy) across five experimental groups: single-beam UHDR, two-beam UHDR, six-beam UHDR, twelve-beam UHDR, and conventional dose rate (CDR). To evaluate normal tissue toxicity, a skin damage cohort was monitored photographically for four weeks post-irradiation, with acute reactions evaluated by a trained observer. In a separate cohort, real-time tissue oxygenation (pO_2)was tracked via a fiber-optic phosphorometer using the phosphorescent probe Oxyphor PtG4 to evaluate physiological kinetics independently of the longitudinal toxicity study.

Results: The FLASH skin-sparing effect was preserved for all UHDR configurations at the 23.6 Gy and 25.2 Gy dose levels. Mixed-effects regression analysis demonstrated that all four UHDR groups developed significantly lower skin toxicity scores compared to the CDR group ($p < 0.05$). At the highest dose level (25.9 Gy), no significant differences were observed among any radiation groups, which was attributed to a saturation effect of the visual skin score assay at severe damage thresholds. The thirteen cohort revealed that the rate of tissue oxygen resupply progressively accelerated over the course of treatment, demonstrating an acute physiological response driven by localized concentration gradients, vasodilation, and capillary recruitment.

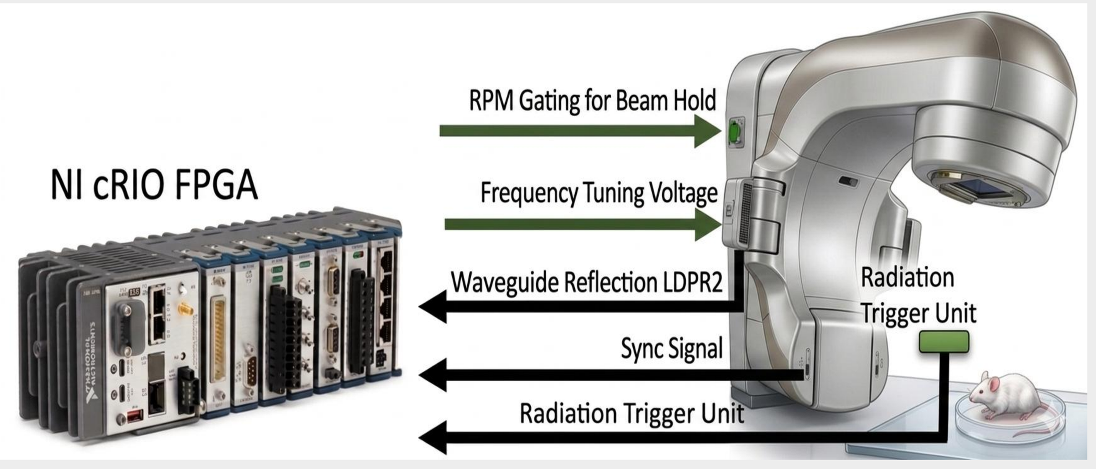
Conclusions: This study represents a promising step toward UHDR multi-beam delivery, a prerequisite for clinical conformal treatment planning. Multiple UHDR fields delivered within five seconds provide an identical degree of normal tissue sparing as a single UHDR beam. Furthermore, the observed tissue oxygen dynamics reveal an acute biological response potentially unique to UHDR delivery, shedding light on a novel physiological component of the FLASH mechanism.

INTRODUCTION

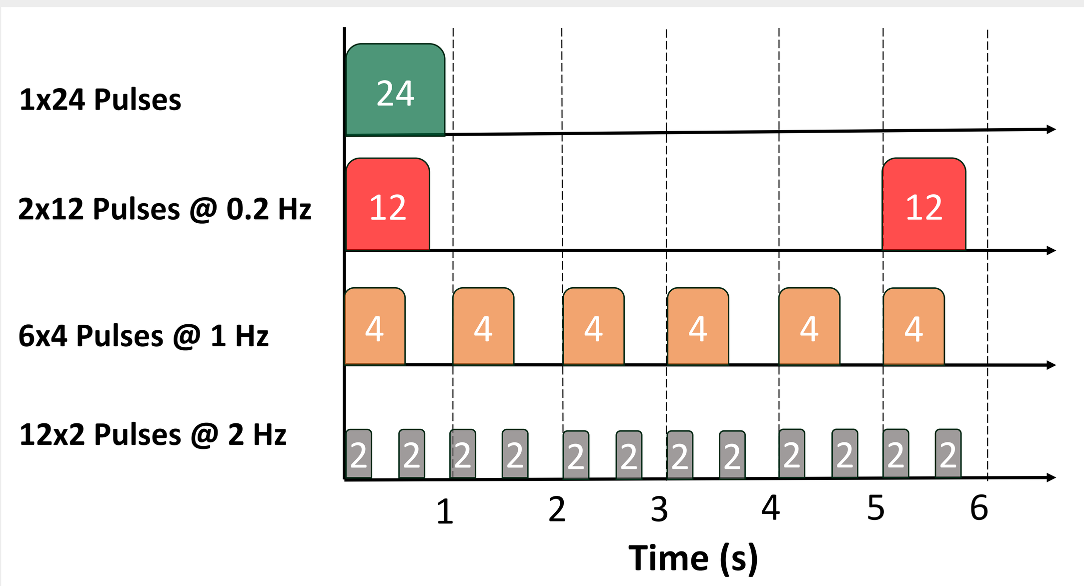
FLASH Radio Therapy (FLASH-RT) is an emerging RT technique that utilizes ultra-high-dose-rates (UHDR) to spare normal tissue while maintaining tumor control. However, there are two main challenges FLASH-RT faces before entering common clinical practice: many FLASH-RT studies use high single dose deliveries unsuitable for direct clinical translation. Secondly, the mechanisms responsible for the FLASH effect remain poorly understood. This study examines the feasibility and tissue oxygen dynamics of multiple low-dose UHDR beams, setting the foundation for future conformal delivery.

METHODS AND MATERIALS

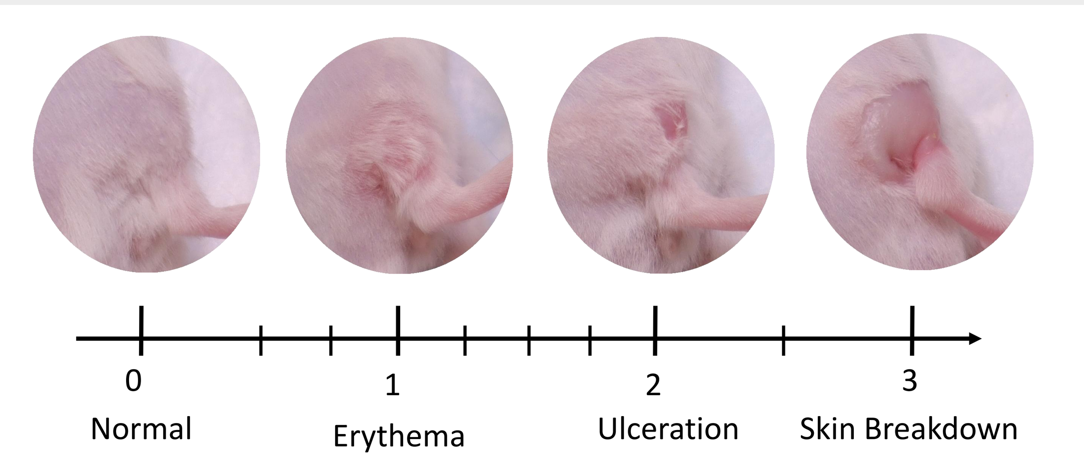
Linac Beam Timing Control System



Multi-Beam Skin Scoring UHDR Delivery Diagram



Skin Scoring Progression

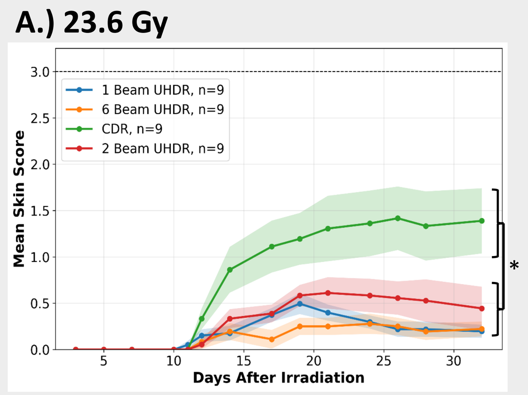


Murine skin reaction scoring scale	
Score	**Narrative Description**
0.00	**Normal appearance; no visible changes**
0.50	Questionable change; difficult to distinguish from normal
0.75	Mild abnormality; subtle changes visible
1.00	**Clear abnormality with erythema (reddening)**
1.25	Pronounced erythema with white flaky skin and/or edema
1.50	Localized moist desquamation in a very small area with scaly or crusty appearance
1.75	Multiple small areas of moist desquamation
2.00	**Extensive area breakdown with moist regions (ulceration)**
2.50	Large confluent areas of moist desquamation with exudate
3.00	**Severe skin breakdown affecting majority of irradiated area with extensive moist exudate**

RESULTS

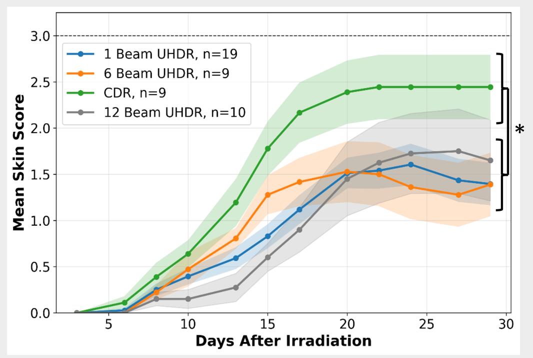
1, 2, 6, or 12 UHDR beams delivered within five seconds all produce equivalent normal tissue sparing.

A.) 23.6 Gy



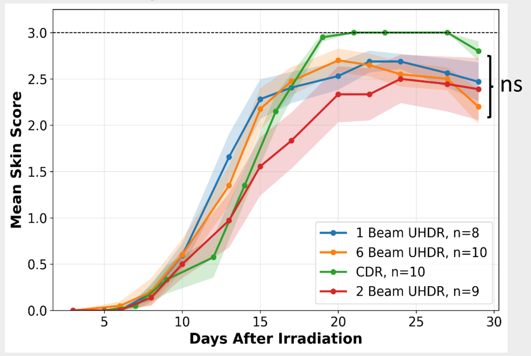
Statistical P-Values		
23.6 Gy		
Delivery	1 Beam UHDR	CDR
1 Beam UHDR	--	p=0.000*
2 Beam UHDR	p=0.463	p=0.004*
6 Beam UHDR	p=0.715	p=0.000*

B.) 25.2 Gy

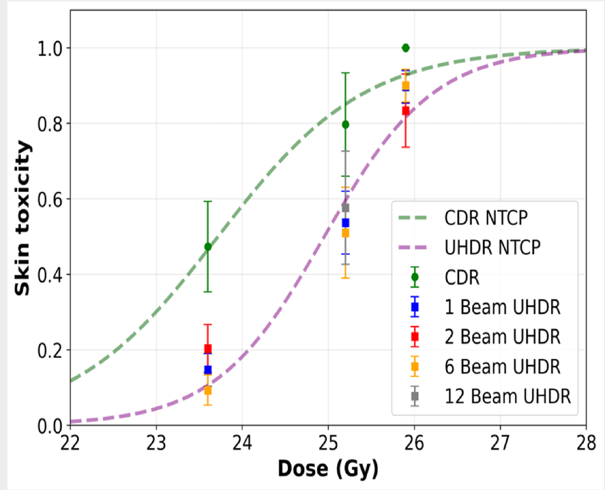


Statistical P-Values		
25.2 Gy		
Delivery	1 Beam UHDR	CDR
1 Beam UHDR	--	p=0.008*
6 Beam UHDR	p=0.851	p=0.035*
12 Beam UHDR	p=0.868	p=0.014*

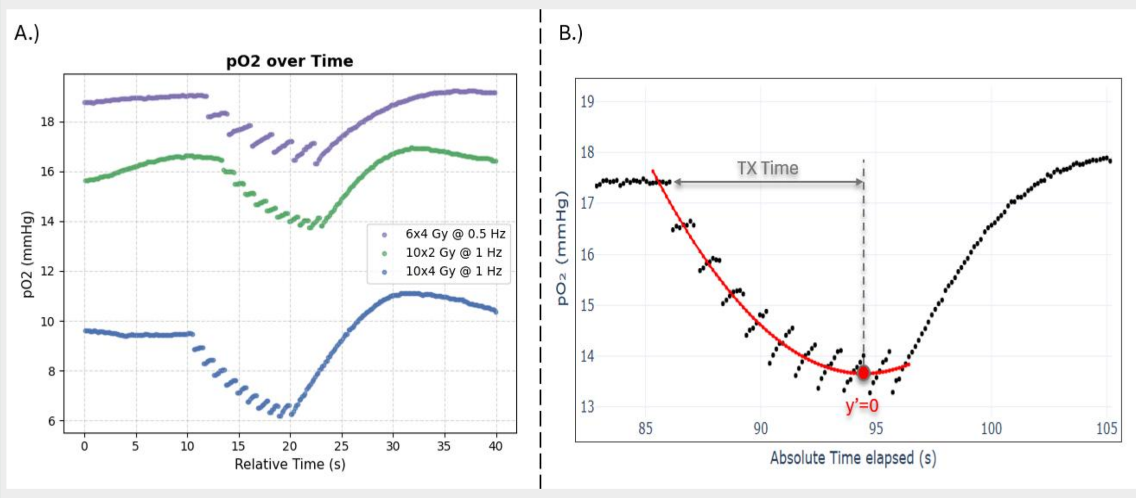
C.) 25.9 Gy

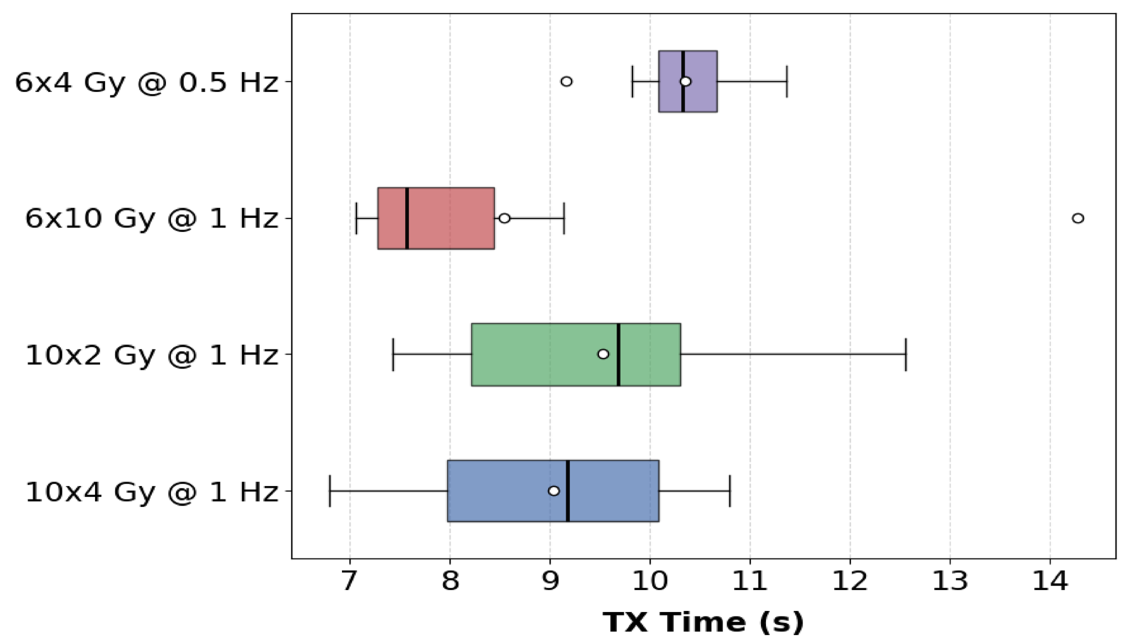


Statistical P-Values		
25.9 Gy		
Delivery	1 Beam UHDR	CDR
1 Beam UHDR	--	p=0.706
2 Beam UHDR	p=0.152	p=0.260
6 Beam UHDR	p=0.769	p=0.929

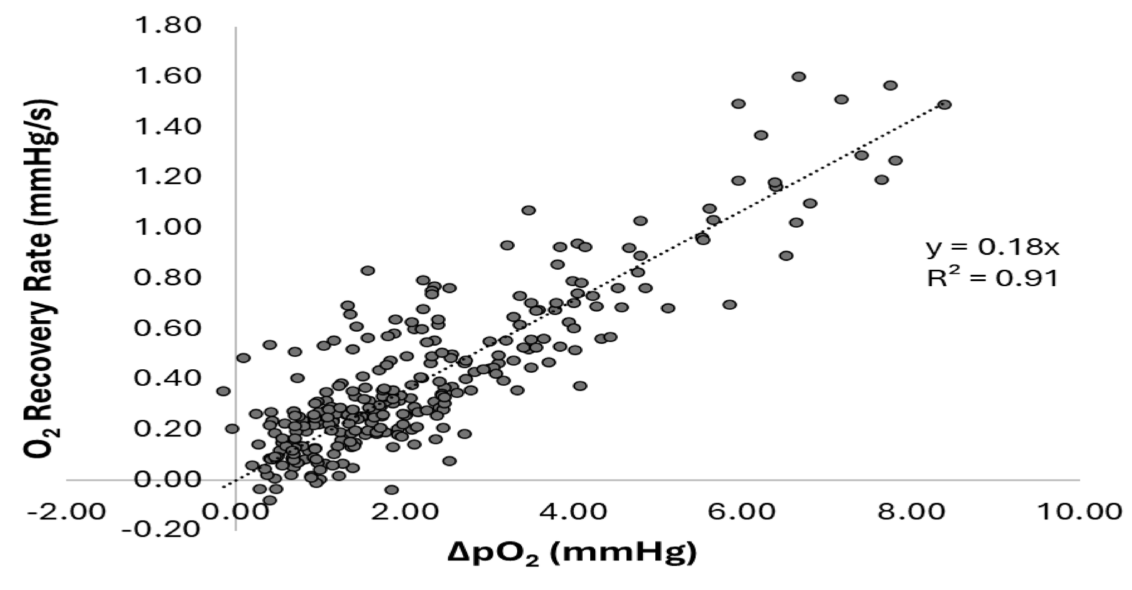


The rate of pO_2 resupply increases over the course or treatment and equilibrates with ROC after 7-11 seconds.

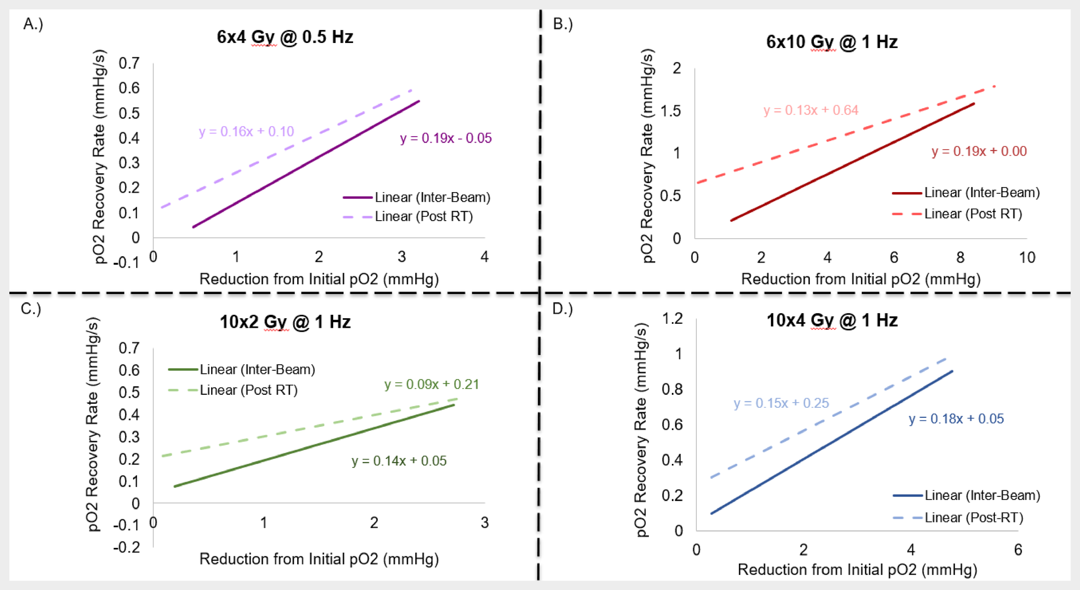




The increase in pO2 resupply is primarily due to diffusion concentration gradients.



The increase is greater than can be attributed to gradients alone, suggesting an additional biological response - vasodilation and capillary recruitment.



DISCUSSION

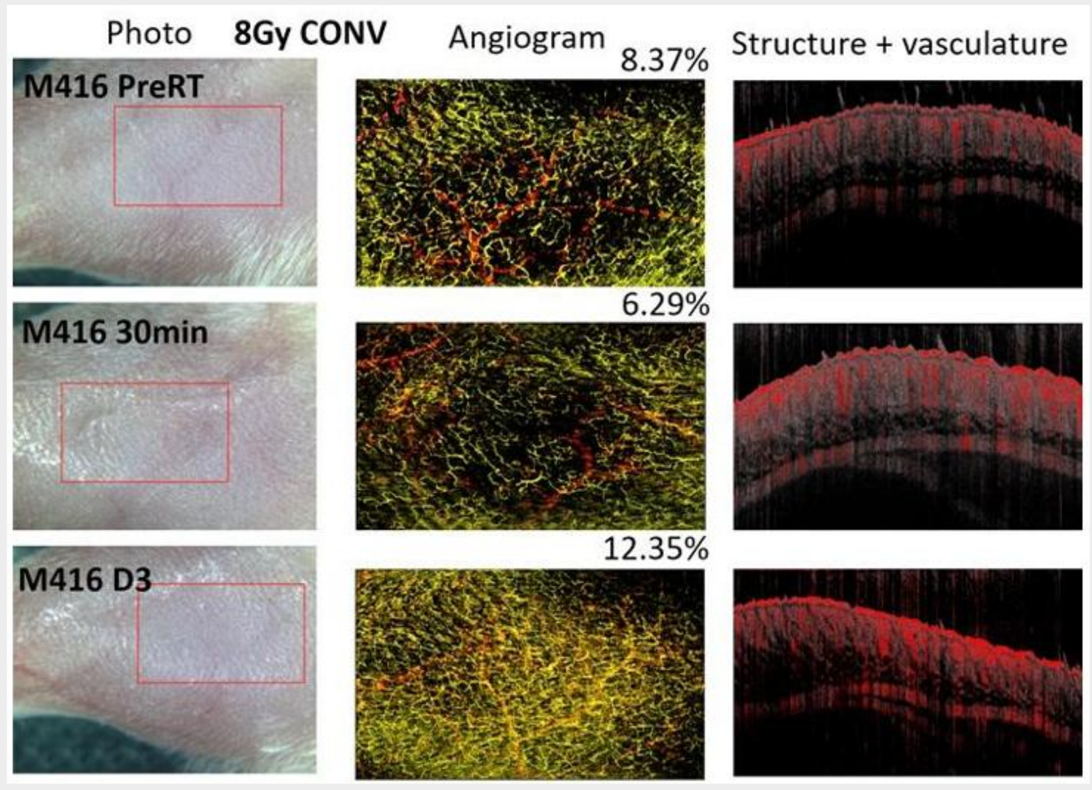
This work provides the first evidence that FLASH sparing is preserved with up to twelve UHDR beams delivered within five seconds. Multiple UHDR beams expand the possibility for eventual conformal UHDR delivery with photon beams and lower doses to healthy tissues.

This work also demonstrates that UHDR irradiation induces transient acute hyperemia, a biological response potentially unique to FLASH-RT. Tissue pO_2 measurements are only a surrogate for this response which affects many other physiological processes in addition to oxygen diffusion.

Together, these findings address the high dose limitation of FLASH-RT and shed light on potential tissue sparing mechanisms; small steps towards the clinical application of FLASH-RT.

Future Work

We hope to repeat these findings using a photon FLASH beam to achieve true conformality. We also plan on studying acute microvascular response to CDR and UHDR irradiation, providing insight into potential vasodilation and capillary recruitment.



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1. J. P. Sunnerberg *et al.*, "Timescale of FLASH sparing effect determined by varying temporal split of dose delivery in mice," *Int. J. Radiat. Oncol.*, Oct. 2025, doi: 10.1016/j.ijrobp.2025.09.052.
2. B. W. Pogue, D. Hunter, C. Narita, W. Thomas, X. Cao, and H. Swartz, "Review of oxygen measurement and relevance to the mechanisms of FLASH radiotherapy," *Front. Phys.*, vol. 14, Jun. 2026, doi: 10.3389/fphy.2026.1878483.

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