Early Detection of FLASH Dose Rate-Dependent Radiation Skin Response

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INTRODUCTION

This study investigated the early microscopic markers for radiation-induced damage prior to the observable toxicity for conventional or ultrahigh dose rate FLASH radiotherapy (CDR/UHDR RT). FLASH radiotherapy produced a significant reduction in radiation-induced normal tissue toxicity at isodose levels when compared to CDR RT, while maintaining the tumor control. The mechanism behind the so-called FLASH effect is still unclear, and none of the existing hypotheses are conclusively proven, yet factors such as tissue oxygenation and cellular metabolism can definitely affect the outcomes. We aim to understand the processes occurring before the radiation toxicity is present and establish the biomarkers responsible for FLASH tissue sparing

METHODS

- IntraOp Mobetron 9 MeV Electrons
  - Dosimetry
    - EBT-XD Gafchromic film
    - PTW flashDiamond
    - UHDR: 360 Gy/s, ~3 Gy per pulse, 90Hz
    - CDR: 0.16 Gy/s
- Irradiation Set up
  - C57Bl/6 female mice, 10-12 weeks old
  - Immobilized via 3D printed Jig
  - Dose groups: 20 Gy, 24 Gy, 27 Gy

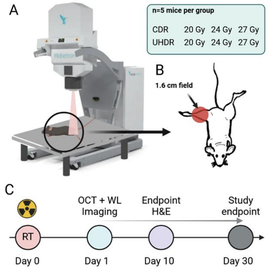


Figure 1. A) Mouse Radiation setup showing the mouse positioning sketch and the study design with the doses and dose groups. **B)** Mouse position under the electron beam. Circle area indicates the irradiation field of 1.6 cm. **C)** Timeline of the experiment for the longitudinal follow-up via OCT imaging every other day with the 10 days endpoint

RESULTS

- Visual skin damage scores increased gradually and showed clear dose dependence. However, increases in visual scores consistently lagged behind OCT-derived thickness changes.
- Figure 2 demonstrates a timeline for one of the mice receiving 24 Gy CDR RT. The white light photographs on the right show that no ulceration was observed until day 13 post-RT; however the microscans obtained with OCT demonstrate a clear change in skin architecture.
- From Figures 2 and 3 we can observe that while the skin architecture started changing as early as day 8 post irradiation, the visible damage was lagging five days behind.
- Figure 4 demonstrates the comparison of various histological metrics following 10 days of the irradiation of CDR/UHDR cohorts
- We observe the increased sparing of sebaceous glands following the UHDR irradiation compared to an almost complete disappearance after CDR irradiation.
- Other markers of radiation dermatitis like vacuolar degeneration or dyskeratosis, demonstrate an increased trend towards CDR cohort

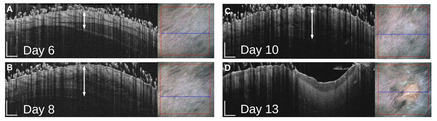


Figure 2. Timeline covering the span of 6-13 days post-RT for a mouse receiving 24 Gy CDR

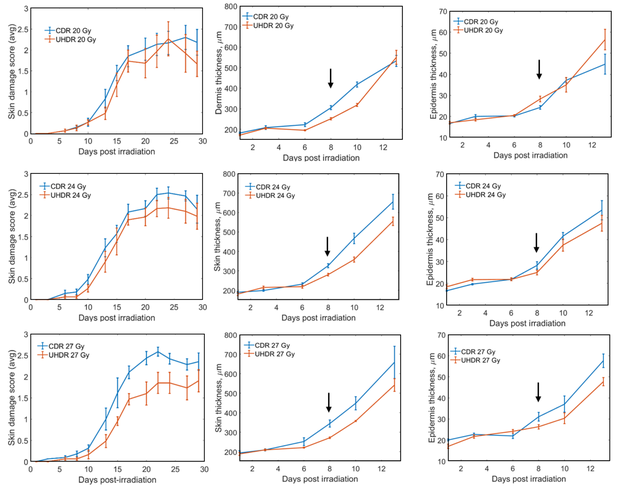


Figure 3. Side-by-side comparison of the skin damage change (left column), dermal thickening (middle column), and epidermal thickening (right column) following 27, 24, and 20 Gy RT. The arrows demonstrate the start of the epidermal and dermal thickening occurring preceding the visual damage

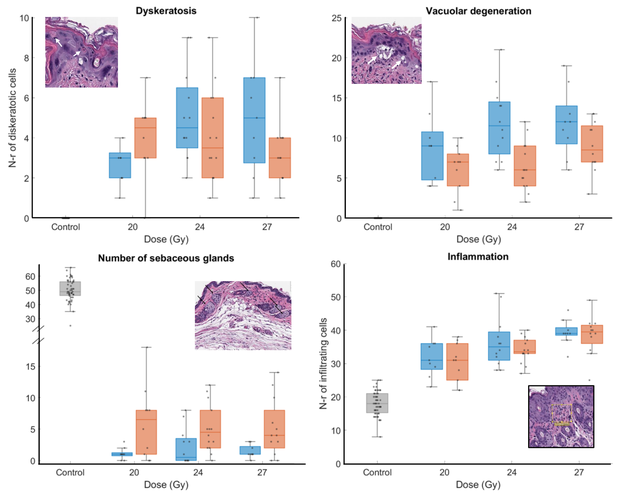


Figure 4. Histological markers demonstrating the difference between control (non-irradiated) mice and mice receiving various doses at CDR and UHDR. The insets on the plots illustrate an example of the quantifying metric.

CONCLUSIONS

We detected measurable changes in epidermal and dermal thickness during the early post-irradiation period, preceding the onset of visually detectable skin damage. We observe an early dermal and epidermal thickening occurring in early pre-toxicity stages. Thickness dynamics were dose dependent and exhibited clear differences between FLASH and conventional irradiation. H&E results demonstrate the different rate of sebaceous glands sparing and vacuolar degeneration between CDR and UHDR cohorts.

The combination of OCT and H&E represent sensitive quantitative metrics for investigating radiation skin response and emerging dose-rate effects. This combined study helps us better understand the early changes that potentially contribute to the understanding of the FLASH effect

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