

## BIOLOGY CONTRIBUTION

# Minibeam Radiation Therapy Valley Dose Determines Tolerance to Acute and Late Effects in the Mouse Oral Cavity

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**Purpose:** Minibeam radiation therapy (MBRT) is an innovative strategy to improve normal tissue sparing by delivering alternating, submillimeter-wide regions of high “peak” and low “valley” doses. The purpose of this study was to characterize both acute and late MBRT-induced normal tissue toxicities and determine the dosimetric parameters that dictate toxicity.

**Methods and Materials:** Mice were stratified by weight and randomized to receive a single dose of conventional radiation therapy (uniform open field) or MBRT (0.5 mm-wide minibeam spaced 1.1 mm center to center) to the oral cavity. The conventional RT groups (n = 4 per group) received 16 or 20 Gy, whereas the MBRT groups (n = 5 per group) received peak:valley doses of 48:8, 72:12, 96:8, 96:16, or 152:8 Gy. Acute toxicity ( $\leq 3$  weeks) was evaluated using changes in weight and mucosal histology. Late effects on bone and dentition were evaluated using microscopic computed tomography (microCT).

**Results:** Animals irradiated with 16 Gy (n = 1), 20 Gy (n = 4), and 96:16 Gy (n = 5) reached acute toxicity endpoint ( $\geq 20\%$  weight loss) between 9 and 11 days postradiation and exhibited histologic changes indicative of mucositis. No animals in the other MBRT groups reached acute toxicity endpoint. Although 96:8 Gy induced marked mucosal damage in peak regions, the spared tissue in the valley regions enabled restoration of mucosal integrity within 2 weeks post-MBRT. MicroCT of surviving mice 12 months postradiation revealed an alternating pattern of decreased bone volume consistent with the MBRT pattern. The upper incisors of most animals were shortened or completely missing. The mice receiving 16 Gy and 48:8 Gy exhibited the most and least dental damage, respectively.

**Conclusions:** This preliminary study emphasizes that normal tissue sparing by MBRT, as determined by the valley dose, significantly ameliorates dose-limiting toxicities and enables escalation to MBRT peak doses up to an order of magnitude greater than conventional RT doses. © 2025 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

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## Introduction

Spatially fractionated radiation therapy (SFRT) exploits the dose-volume effect and reduces the volume of tissue receiving high doses by dividing the primary radiation beam into alternating regions of high “peak” and low “valley” doses. Therefore, SFRT presents a strategy to improve normal tissue sparing and simultaneously enable dose escalation.<sup>1</sup> There has long been interest to deliver SFRT with submillimeter spatial dimensions. Several preclinical studies have demonstrated promising antitumor effects and normal tissue sparing with so-called minibeam RT (MBRT)<sup>2-4</sup> and microbeam RT techniques.<sup>5-8</sup>

In this preliminary study, a small animal irradiator was used to deliver heterogeneous doses of MBRT and uniform doses of conventional RT to the mouse oral cavity. Our results demonstrate that MBRT peak doses up to an order of magnitude greater than conventional RT doses are tolerable, provided that the valley dose is sufficiently low. The low energy x-rays used for MBRT may be well suited for head and neck cancers because of their relatively superficial location. Accordingly, characterizing the radiation tolerance of critical structures in this region may be helpful for future radiobiological studies as well as clinical application of MBRT to head and neck cancers.

## Methods and Materials

Nontumor bearing mice ( $n = 33$ ) were stratified by weight and randomized across groups receiving a single fraction of conventional RT (16 or 20 Gy;  $n = 4$  per group) or MBRT (peak:valley dose of 48:8, 72:12, 96:8, 96:16, or 152:8 Gy;  $n = 5$  per group) to the oral cavity. Conventional RT was delivered with a single posterior-anterior, 10-mm circular open field encompassing the oral cavity and oropharynx. MBRT was delivered with the same arrangement, but the field was further collimated using custom-made multislit tungsten collimators to produce  $0.5 \pm 0.05$ -mm-wide minibeam spaced  $1.1 \pm 0.05$  mm center to center (Fig. 1). Acute toxicity was defined as a reduction in weight  $\geq 20\%$  (compared with pretreatment) within the first 3 weeks post-RT and confirmed with histologic analysis of tongue tissues. To evaluate late effects, surviving animals were followed for 12 months and evaluated for dental and bone changes using microscopic computed tomography (microCT). Additional details of animal procedures, radiation delivery, and evaluation of acute and late toxicity are included in the supplementary material.

## Results

### **MBRT mitigates acute radiation-induced toxicity**

The 20-Gy conventional RT and the 96:16 Gy MBRT doses were highly toxic, with all animals in these groups reaching

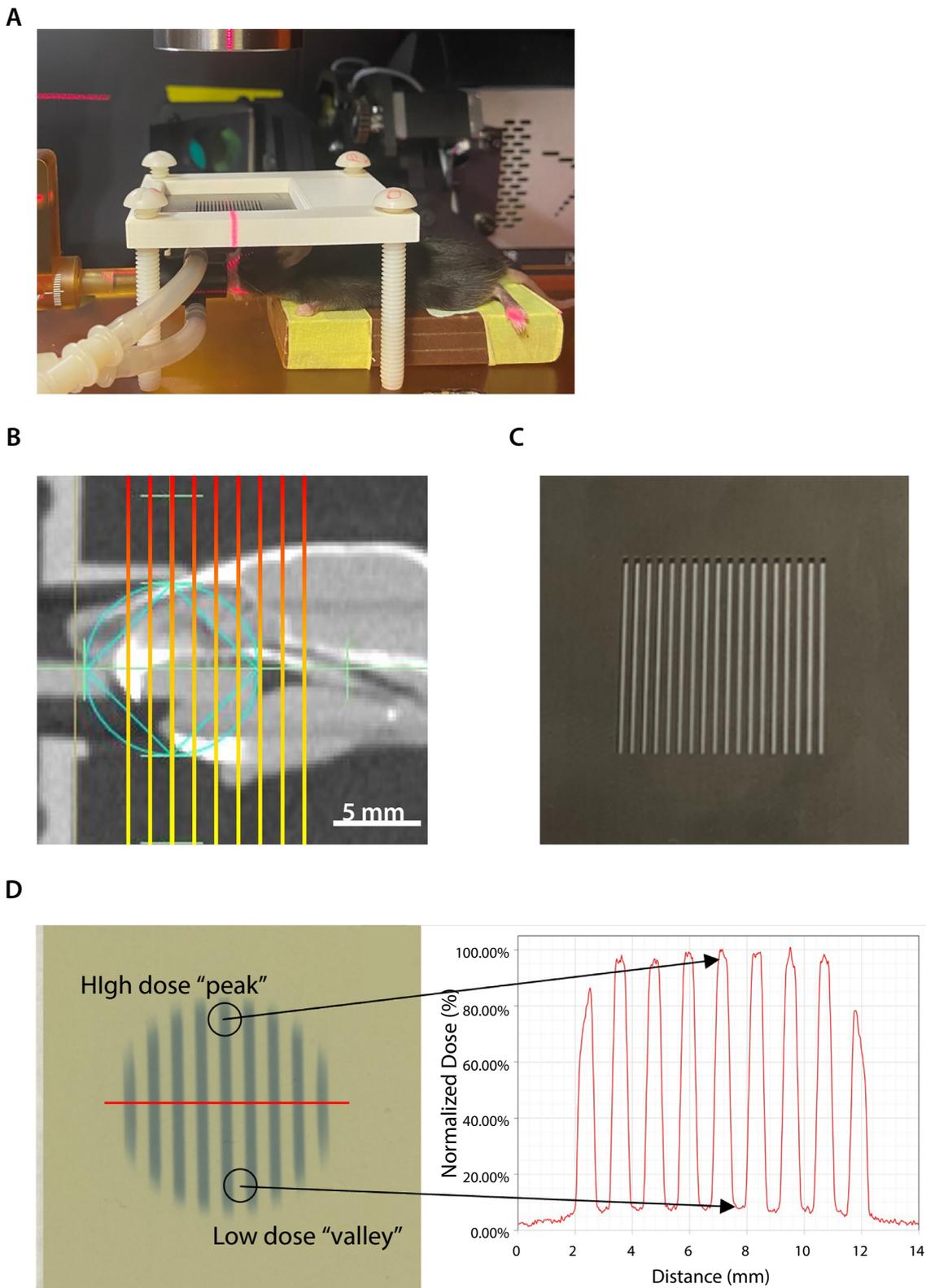
the acute toxicity endpoint between 9 and 11 days post-RT (Table 1). One animal that received 16-Gy conventional RT also reached acute toxicity endpoint. In contrast, no animals in the 4 other MBRT groups (48:8, 72:12, 96:8, and 152:8 Gy) reached the acute toxicity endpoint, despite the larger mean doses compared with conventional RT. The relative weights of all surviving animals returned to baseline within 20 days post-RT (Fig. 2A). Compared with 96:16 Gy, animals that received the same peak dose of 96 Gy but a lower valley dose of 8 Gy (96:8 Gy) exhibited significantly less weight loss and recovered to pretreatment weight by day 14. Interestingly, the mice irradiated with a valley dose of 8 Gy (48:8, 96:8, and 152:8 Gy) presented similar weight loss and weight gain patterns, despite the increasing peak and mean doses. However, increasing the valley dose from 8 to 12 to 16 Gy with a constant peak-to-valley dose ratio of 6 (48:8, 72:12, and 96:16 Gy, respectively) resulted in increased weight loss (Fig. 2B). Although the mean dose was nearly 20 Gy higher in the 152:8 Gy group than in the 96:16 group, all of these animals survived and recovered. In contrast, the lower mean dose, but higher valley dose, associated with the 96:16 group was prohibitively toxic.

### **Oral mucosal histologic changes associated with radiation toxicity**

Compared with the unirradiated tongue, conventional RT delivering 20 Gy resulted in extensive damage to the mucosal epithelium at day 10 (Fig. 3A, B). Significant epithelial loss extended from the tip of the tongue to the dorsal surface, with loss of dermal and keratinized filiform papillae. Compared with this 20-Gy dose, the tissue irradiated with 16-Gy conventional RT exhibited reduced epithelial loss, localized to the tip of tongue (day 11, Fig. 3C). The majority of the dorsal surface retained a thickened epithelium, exhibiting occasional keratinization, filiform papillae, and irregular dermal papillae. When delivered in an MBRT configuration, a 16-Gy valley dose with a 96-Gy peak dose produced more pronounced mucosal alterations (day 11, Fig. 3D) than 16-Gy conventional RT but less pronounced than 20-Gy conventional RT. In contrast to 96:16 Gy, the tissue irradiated with 96:8 Gy maintained epithelial stratification with an intact basal layer and dermal papillae but with some thickening and discontinuity in the keratinized layer (day 10, Fig. 3E). The marked epithelial denudation observed in these tissues confirms the association of acute weight loss with histologic changes characteristic of oral mucositis. These results support the concept that a lower valley dose provides mucosal sparing, which enables higher radiation tolerance and extended survival despite large MBRT peak doses.

### **Restoration of the mucosal epithelium after MBRT**

The epithelium exhibited discontinuity and thinning 6 days after 96:8 Gy (Fig. 4A). Damage progressed by day 8



**Fig. 1.** Radiation delivery setup. (A) Mice were anesthetized and positioned using a bite block in the SmART+ PXI small animal stereotactic irradiator. All radiation was delivered using a posterior-anterior 10-mm circular x-ray beam. (B) Cone beam computed tomography was used for targeting and peak radiation dose was prescribed at 5 mm depth. (C) For minibeam radiation therapy (MBRT), the beam was spatially fractionated into 0.5-mm-wide minibeams spaced 1.1 mm center to center using tungsten collimators. (D) Representative dose profile of the MBRT setup was obtained using radiochromic film.

**Table 1** Summary of treatment groups and timing of the observed toxicity endpoint for each animal

Acute toxicity			
Dose (sample size)	Mean dose (Gy)	Rate of toxicity	Day(s)
16 Gy <sup>a</sup> CRT (n = 4)	16 ± 0.2	1/4	11
20 Gy <sup>a</sup> CRT (n = 4)	20 ± 0.3	4/4	10, 10, 11, 11
48:8 Gy <sup>b</sup> (n = 5)	25 ± 0.6	0/5	-
72:12 Gy <sup>b</sup> (n = 5)	37 ± 0.9	0/5	-
96:8 Gy <sup>c</sup> (n = 5)	45 ± 1.1	0/5	-
96:16 Gy <sup>b</sup> (n = 5)	49 ± 1.2	5/5	9, 9, 10, 10, 11
152:8 Gy <sup>d</sup> (n = 5)	68 ± 1.7	0/5	-
Late toxicity			
Dose (sample size)	Mean dose (Gy)	Rate of toxicity	Day(s)
16 Gy <sup>a</sup> CRT (n = 3)	16 ± 0.2	1/3	322
48:8 Gy <sup>b</sup> (n = 5)	25 ± 0.6	0/5	-
72:12 Gy <sup>b</sup> (n = 5)	37 ± 0.9	3/5	191, 289, 289
96:8 Gy <sup>c</sup> (n = 5)	45 ± 1.1	0/5	-
152:8 Gy <sup>d</sup> (n = 5)	68 ± 1.7	1/5	226

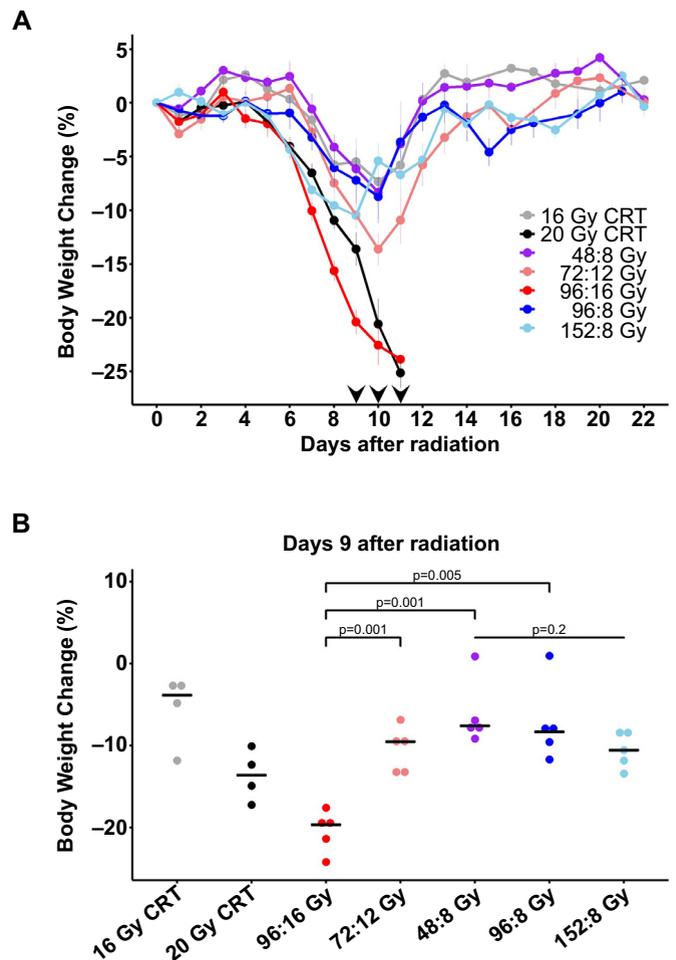
Mean dose represents the average dose within a 1-cm diameter circular region of interest on 3 films irradiated at 5-mm depth for each collimator thickness. Acute toxicity was defined as a relative body weight change  $\geq 20\%$  (compared with pretreatment) within the first 3 weeks postradiation. Late toxicity was defined as a relative body weight change  $\geq 15\%$  (compared with pretreatment) accompanied by moribund behavior at 3 weeks or later post-RT. Relative uncertainty (measurement standard deviation divided by the measured value, expressed as a percentage):

<sup>a</sup> 1.3%.  
<sup>b</sup> 2% (peak) and 2.7% (valley).  
<sup>c</sup> 2.6% (peak) and 1.8% (valley).  
<sup>d</sup> 2.1% (peak) and 2.2% (valley).

(Fig. 4B), resulting in complete loss of epithelium in some regions. By day 10 (Fig. 4C), the stratified epithelium was present on the majority of the dorsal surface and filiform papillae began to regenerate by day 12 (Fig. 4D). Epithelial thickness and stratification returned almost to normal by day 14 (Fig. 4E).

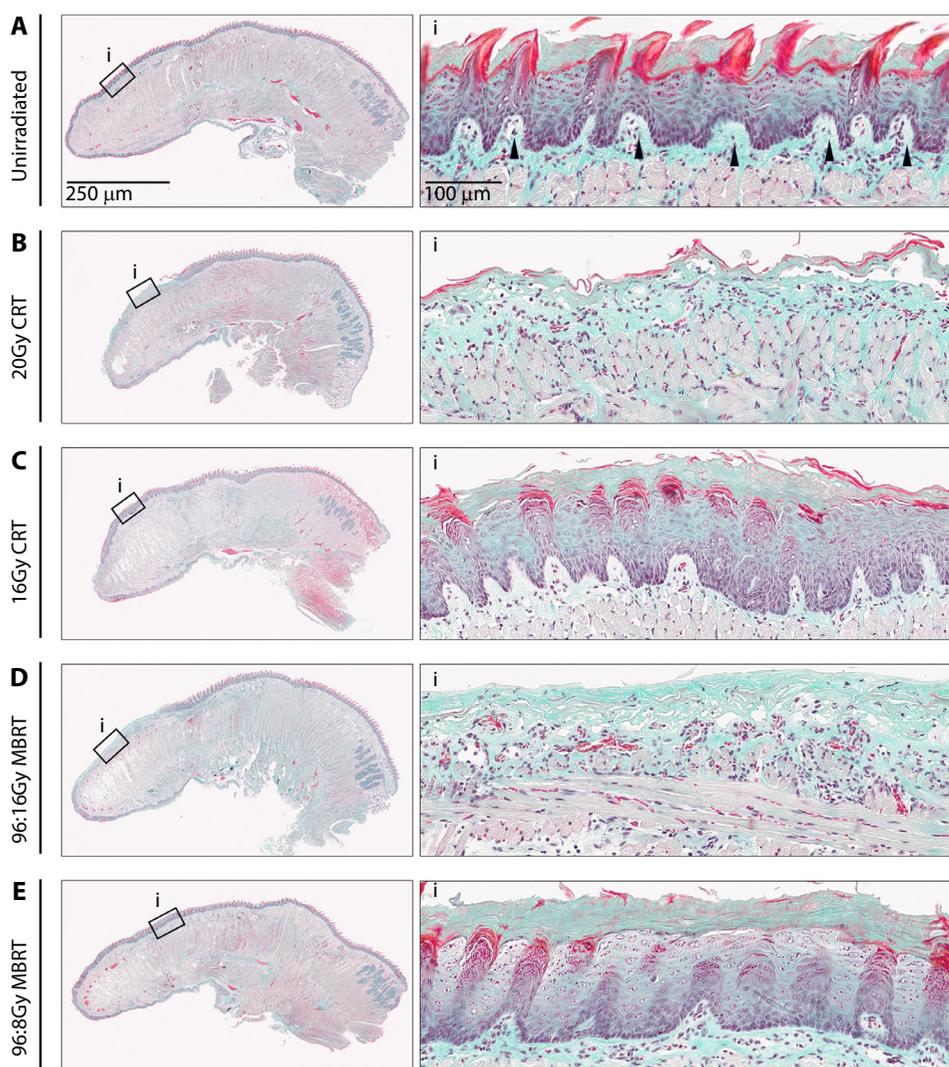
### MBRT mitigates late radiation effects on bone and dentition

To assess potential late radiation effects, animals that did not meet humane endpoint were followed for 12 months after RT and evaluated for dental and bone changes. Three weeks post-RT, surviving mice returned to baseline weight and steadily gained weight in the following months. Between 6 and 10 months after RT, some animals receiving 72:12 Gy (n = 3), 152:8 Gy (n = 1), and 16 Gy (n = 1) lost  $\geq 15\%$  weight and required euthanasia (Table 1). In these animals,



**Fig. 2.** Acute changes in body weight after radiation. (A) Changes in body weight relative to pretreatment (day 0) were used as a surrogate for oral mucositis after minibeam radiation therapy (MBRT) or conventional RT (CRT). Plotted data are the mean  $\pm$  standard error. The acute toxicity endpoint was defined such that mice losing  $\geq 20\%$  body weight were humanely euthanized. Animals were euthanized when they reached humane endpoint on days indicated by arrows: day 9 (96:16 Gy, n = 2), day 10 (20 Gy CRT, n = 2; 96:16 Gy, n = 2), and day 11 (16 Gy CRT, n = 1; 20 Gy CRT, n = 2; 96:16 Gy, n = 1) postradiation. (B) Relative weights on day 9 post radiation. Horizontal bars are the median of each group. Analysis of variance was used to make comparisons across more than 2 groups and the two-sample *t* test was used to make comparisons between 2 groups.

the upper incisors were almost nonexistent, and the lower incisors had overgrown. At 12 months all surviving mice underwent microCT imaging. Mice irradiated with MBRT exhibited alternating regions of high and low bone volume, which mirrored the alternating pattern of valley and peak doses (Fig. 5A, B). The MBRT groups that received 8-Gy valley dose had the greatest bone volume per slice, whereas



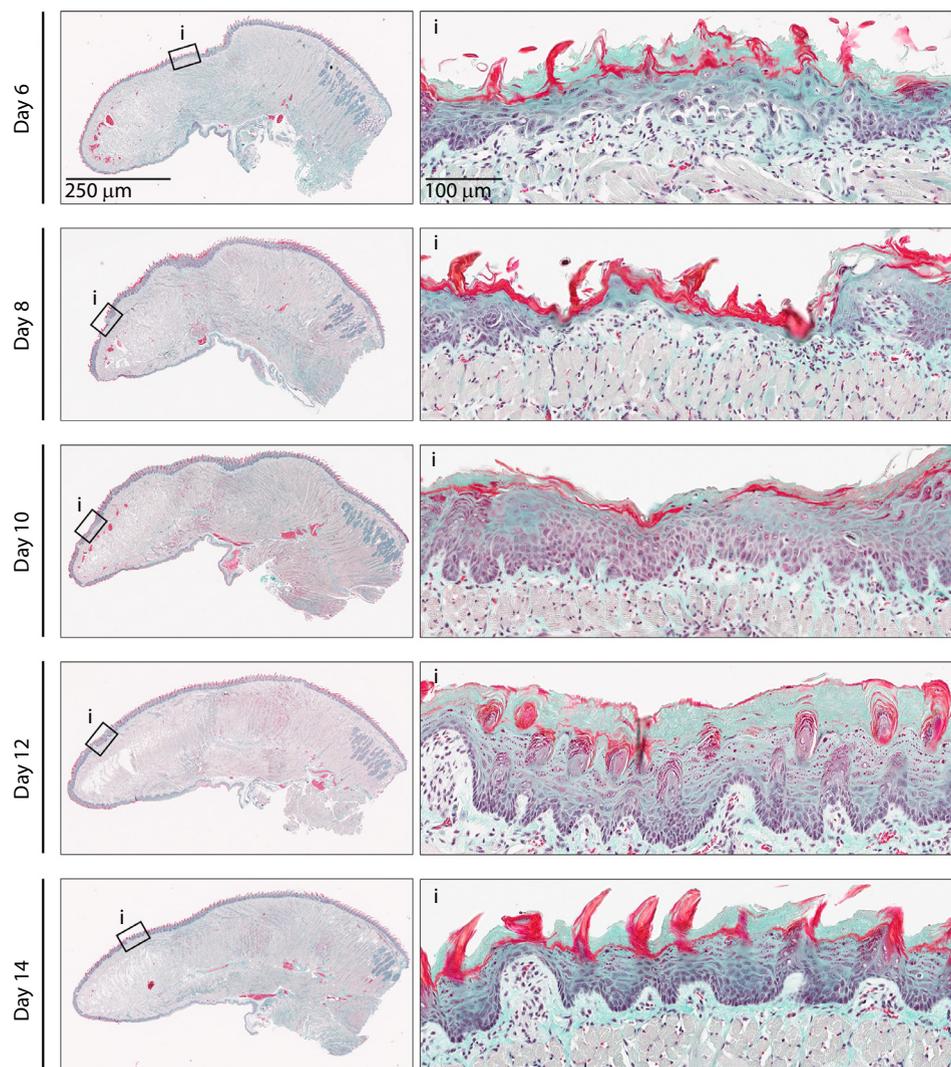
**Fig. 3.** Histologic changes in the oral mucosa of harvested tongue tissues. (A) Tissue from an unirradiated control with dense stratified epithelium and a clear delineation of the basal cell layer (dark purple stain) from the striated muscle (light purple stain) with regular dermal papillae (arrowheads) projecting into the epithelium as well as regular keratinized filiform papillae (red stain). Tissues from animals irradiated with (B) 20-Gy conventional RT, (C) 16-Gy conventional RT, and (D) 96:16 Gy MBRT harvested when toxicity endpoint was met (days 10, 11, and 11, respectively) and (E) 96:8 Gy harvested at 10 days post-MBRT. *Abbreviation:* MBRT = minibeam radiation therapy.

the 72:12 Gy and 16 Gy conventional RT had lower and similar values (Fig. 5C). Furthermore, animals irradiated with 16-Gy conventional RT had the most extensive dental damage, including loss of maxillary incisors and damage to the root (Fig. 5D). In contrast, mice irradiated with MBRT exhibited fewer dental-related effects even with the highest peak dose of 152 Gy and highest mean dose of 68 Gy.

## Discussion and Conclusion

In this study, we evaluated MBRT as a strategy to escalate radiation dose while limiting acute and late toxicities typically associated with conventional RT to the oral cavity. In the acute timeframe, a sufficiently low MBRT valley dose

(8 Gy) enabled the delivery of tolerable MBRT peak doses up to an order of magnitude greater than toxic conventional RT doses. The superior tolerance to MBRT compared with conventional RT was attributed to mucosal sparing in the valley regions, which was followed by restoration of the mucosal epithelium. After 12 months of follow-up, the MBRT groups with lower valley doses exhibited fewer late bone and dental complications than the groups irradiated with higher valley doses and conventional RT. Our study emphasizes that the valley dose, not the peak dose, is an important consideration to limit acute and late radiation toxicities. Furthermore, conventional dose metrics such as the mean dose may not correlate with toxicity due to the uniquely heterogeneous dose distributions characteristic of MBRT. Our findings along with decades of preclinical



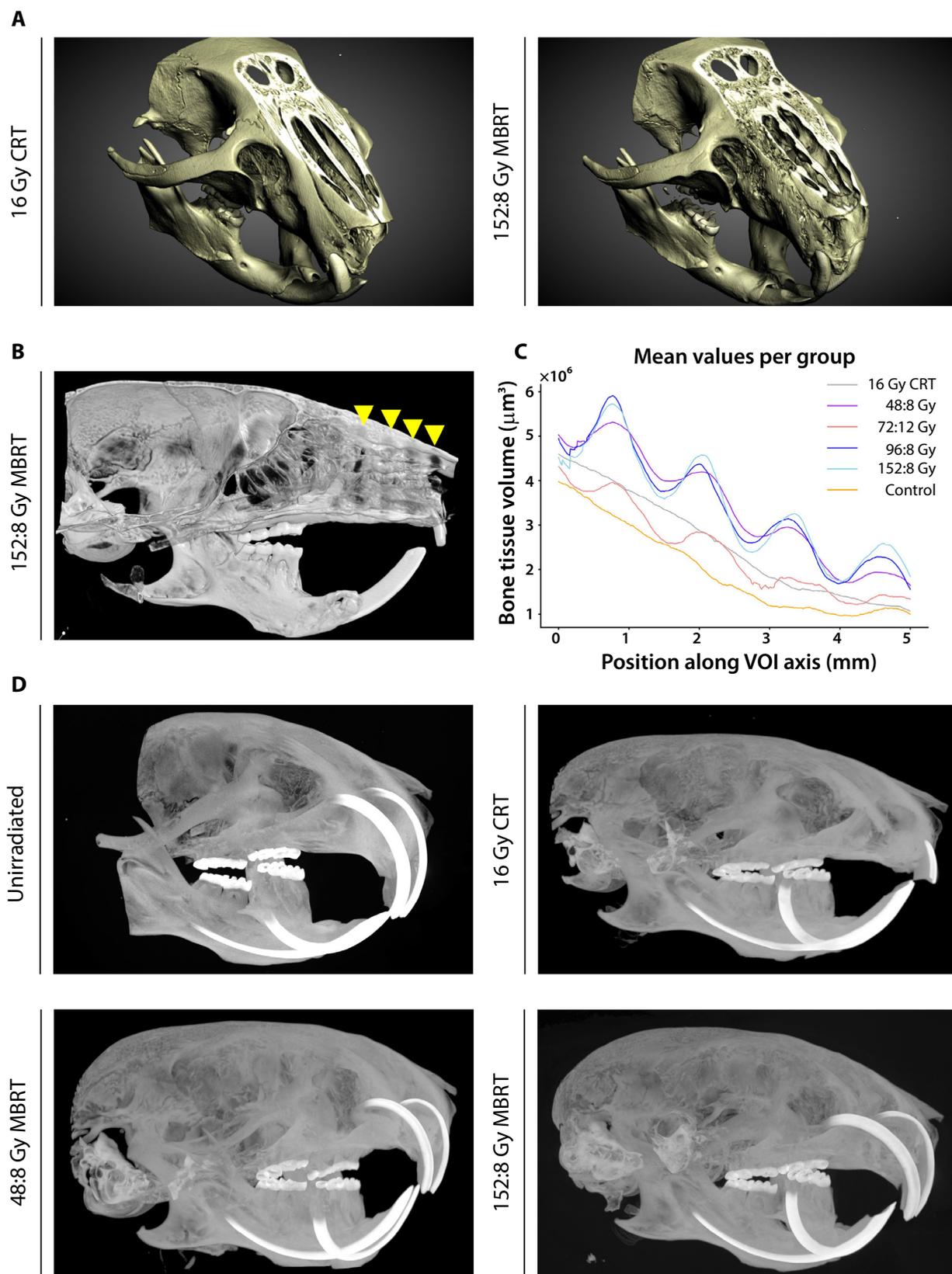
**Fig. 4.** Time progression of histologic changes of the oral mucosa following 96:8 Gy MBRT. (A-E) Tissues collected on days 6, 8, 10, 12, and 14, respectively. *Abbreviation:* MBRT = minibeam radiation therapy.

experience served as convincing evidence for the first ever clinical translation of MBRT<sup>9</sup> and provided rationale for an upcoming phase 1 MBRT dose escalation clinical trial.

The size and spacing of MBRT peak and valley regions permits the application of submillimeter SFRT with commercially available irradiators using clinically feasible dose rates.<sup>10,11</sup> In contrast, microbeam RT generally uses  $\leq 0.1$ -mm-wide beams spaced 0.2 to 0.4 mm apart,<sup>12</sup> which require the use of exceptionally high dose rates ( $>100$  Gy/s) to eliminate blurring of the microscopic dose profile due to target motion.<sup>13</sup> However, such high dose rates are only currently available with synchrotron-based sources found in large national laboratories rather than radiation oncology clinics, making synchrotron x-rays costly and not widely available.<sup>14</sup> Although alternative high dose rate x-ray sources are under development,<sup>15,16</sup> MBRT may have greater translational impact in the near term because wider beam widths (0.5-1 mm) spaced by a few millimeters are less vulnerable to dose blurring from target motion allowing the use of currently available sources.

On irradiation, the restoration of oral mucosal integrity relies on rapidly dividing epithelial stem cells at the basal layer to repopulate the stratified epithelium.<sup>17</sup> The stem cell migration hypothesis poses that a sufficiently wide valley region would spare stem cells, which can migrate and repopulate the damaged peak regions.<sup>18</sup> In line with these concepts, we showed that the regions of epithelial thinning (peak dose regions) regenerated, and the epithelium was restored by day 14 after MBRT. Given that MBRT improved the radiation tolerance (at the organ level) of the oral mucosa relative to conventional RT, we conclude that 0.5-mm minibeam spacing 1.1 mm center to center is an appropriate geometrical setting for the sparing of oral mucosa.

The general increase in bone volume following radiation could potentially be attributed to osteoblastic effects associated with repair and healing over time.<sup>19</sup> In contrast to the oral epithelium where the heterogeneous MBRT damage was restored, the nasal bone retained the alternating MBRT pattern with reduced bone volume in peak dose regions relative to valley dose regions. These results suggest that



**Fig. 5.** Late changes in bone and teeth 12 months after radiation. (A) Representative 3-dimensional rendering of skulls imaged with microCT revealing changes in the nasal bone of animals irradiated with 16-Gy conventional RT and 152:8 Gy MBRT. The microCT reconstruction around part of the skull and the nasal bone regions was intentionally clipped to show changes in the underlying bony anatomy. (B) Sagittal slice with alternating MBRT pattern along nasal bone (arrows). (C) Quantification of bone volume along nasal bone. Error bands corresponding to standard deviations and description of bone quantification included in [Figure E1, E2](#). (D) Volumetric images of skulls of mice receiving no radiation, 16-Gy conventional RT, 48:8 Gy MBRT, and 152:8 Gy MBRT. *Abbreviations:* MBRT = minibeam radiation therapy; microCT = microscopic computed tomography.

osteoprogenitor cells are more radiosensitive than mucosal progenitor cells even at lower valley doses. Nonetheless, the heterogeneous MBRT pattern spared sufficient bone volume to retain structural function. Although enhanced bone dose absorption<sup>20</sup> and prohibitive late effects after 18 Gy (250 kVp x-rays) conventional RT to the oral cavity of mice<sup>21</sup> have been reported, we demonstrated that a sufficiently low valley dose spares late responding tissue, as evidenced by the preserved dental integrity and long-term (12 months) survival of the majority of MBRT-irradiated mice, despite peak doses up to 152 Gy.

Our study has limitations worthy of discussion. First, to modify the peak-to-valley dose ratio while keeping the size and spacing of slits consistent, we employed collimators of different thickness. This results in different energy spectra in the valleys and has implications for the relative biologic effectiveness (RBE), which increases rapidly with decreasing beam energy. Quantifying the RBE in the valleys is a considerable challenge, because it would require a reference photon radiation field having the same characteristics (ie, with the same spectrum) for in vitro studies. Additionally, it is likely the spatial fractionation plays a role in the biologic response,<sup>22,23</sup> and one could not assume the same RBE for the broad reference field applies in a spatially fractionated field of minibeam. Monte Carlo calculations of 3-dimensional dose distributions and RBE may offer relevant insights, but may also have limitations in accurately modeling dose in the valley regions<sup>24</sup> and DNA double strand breaks.<sup>25</sup> A second limitation is the use of only female mice. However, several studies have shown that the strongest level of evidence supports dosimetric parameters, rather than sex differences, as the key predictors of mucositis risk.<sup>26</sup> Finally, the limited sample size used to evaluate late effects and the lack of a tumor model can be considered a limitation. Additional toxicity evaluations remain necessary to fully evaluate the effects of MBRT to the oral cavity. Furthermore, evaluation of efficacy will require longer, larger, and controlled trials and coupling the preliminary toxicity data presented in this study with a similar data set for tumor control is the subject of future work.

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