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# A Comparison of Acute and Late Oral Mucosa Toxicity from Minibeam and Conventional Radiation Therapy

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**Abstract**
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## Abstract

Objectives:

Minibeam Radiotherapy (MBRT) uses kilovoltage x-rays to deliver an alternating pattern of submillimeter wide “peaks” of high dose immediately adjacent to much lower “valley” doses. The resulting heterogeneous dose distribution allows for the delivery of extremely high peak doses, and despite numerous preclinical studies suggesting MBRT may be an effective treatment modality it has not yet translated to patients. Clinical translation of MBRT will require knowledge of potential acute and late toxicities. Oral mucosa is a relevant toxicity model since MBRT may be well suited for head and neck cancers due to the relatively superficial targets. Additionally, mucosal surfaces are found throughout the body in the digestive, respiratory, and reproductive systems. Osteoradionecrosis and dental damage are potential late effects which may arise due to dose enhancement from the kV x-rays. We report on early and late effects between MBRT and conventional radiotherapy (CRT) using an oral mucosa mouse model.

Methods:

33 female C57BLJ6 mice were randomized by body weight (BW) across two CRT groups (n = 4 per group) receiving open field radiation of 16 and 20 Gy and five MBRT groups (n = 5 per group) receiving peak:valley doses of 48:8, 72:12, 96:16, 96:8, and 152:8 Gy. All radiation was given in a single fraction. The CRT groups were irradiated with a 10 mm circular field using a 225 kVp PA x-ray beam encompassing the oral cavity and oropharynx. The MBRT groups were irradiated with the same arrangement, but the x-rays were collimated into 0.5 mm wide minibeams spaced 1.1 mm center-to-center using tungsten collimators of 0.5, 1, and 2.5 mm thickness to deliver peak-to-valley ratios of 6:1, 12:1, and 19:1. As acute oral mucosa toxicity is associated with ulceration and pain leading to decreased nutritional intake, we used changes in BW as a surrogate for oral mucositis. BWs were measured daily starting on the day of treatment, and BW changes were computed relative to the day of treatment. The acute (⩽ 21 days) toxicity endpoint was defined such that mice losing >20% BW were humanely euthanized. The late (>21 days) toxicity endpoint was defined as moribund behavior, including hunched posture and low activity levels, and relative BW loss greater than or equal to 10%. At 12 months, all surviving animals were euthanized and heads harvested for high resolution CT imaging to assess changes in bone density and teeth.

An additional experiment evaluated the acute damage and healing patterns of oral mucosa after MBRT by irradiating 5 mice with a peak:valley dose of 96:8 Gy. These mice were euthanized 6, 8, 10, 12, and 14 days post-treatment and tongues were harvested for histological analysis and compared to an unirradiated control.

Results:

Doses of 20 Gy CRT and 96:16 Gy MBRT were highly toxic, with all animals in these groups reaching the toxicity endpoint between 9-11 days, compared to only one animal in the 16 Gy CRT group, and no animals in the other MBRT groups. The BWs of all surviving animals returned to baseline within 15 days. The groups 48:8, 96:8, and 152:8 Gy showed similar BW loss and recovery patterns for the same valley dose. The groups 48:8, 72:12, and 96:16 Gy showed that, for the same peak to valley ratio, increasing the valley dose resulted in increased BW loss. While animals did not tolerate 96:16 Gy, those in the 96:8 Gy group fully recovered.

Histological staining of the tongues in the 5 additional mice exposed to 96:8 MBRT showed a progression of damage and healing. Six days after MBRT the epithelium showed signs of discontinuity and thinning. Damage progressed by day 8 with some regions showing complete loss of epithelium. By day 10 stratified

epithelium was present on most of the dorsal surface but remained absent from the tip of the tongue. On day 12 stratified epithelium was present on most of the tongue surface. By day 14 epithelial thickness returned almost to normal with the entire tongue surface having complete epithelial coverage.

BWs remained stable or increased in all surviving animals for 6 months. Between 6-11 months 1 mouse in the 16 Gy CRT group, 3 mice in the 72:12 MBRT group, and 1 mouse in the 152:8 MBRT met the late toxicity endpoint. High resolution CT images of the remaining mice at 12 months revealed an alternating pattern of decreased bone density consistent with the dimensions of the MBRT irradiation. The upper incisors of most animals were shortened or completely missing with mice in the 16 Gy CRT arm showing the most damage and mice in the 48:8 MBRT arm showing the least.

Conclusion(s):

Despite extreme acute toxicity caused by 20 Gy CRT, animals in the MBRT groups tolerated peak doses up to 152 Gy when the valley dose was 8 Gy. These results confirm the superior normal tissue sparing capacity and acute toxicity profile of MBRT compared to CRT in an oral mucosa mouse model. Our results suggest that valley dose, not peak dose, is the most relevant parameter in MBRT to assess acute toxicity. Late effects including decreased bone density and dental damage may be relevant for MBRT, but could likely be mitigated with lower peak and valley doses and a fractionated treatment schedule. Our results may prove useful for eventual clinical translation of MBRT in head and neck cancers.