A Histomorphometric Analysis of Parathyroid Hormone Treatment of Radiation Damage in a Murine Model of Distraction Osteogenesis

Purpose: Radiation therapy is known to be detrimental to bone and soft tissue repair, resulting in an unacceptably high incidence of devastating wound healing complications. This is effected through a mechanism of both direct cellular and vascular depletion. We sought to utilize an anabolic regimen of parathyroid hormone (PTH), an FDA-approved bone therapeutic, to remediate this deficiency. The purpose of this study was to allow for the successful utility of distraction osteogenesis in an irradiated field utilizing an intermittent regimen of PTH for the purpose of craniofacial reconstruction in head and neck cancer victims.

Methods: 20 male Lewis rats were randomly split into three groups, DO (n=5), XRT/DO (n=10), and XRT/DO/PTH (n=5). XRT/DO and XRT/DO/PTH underwent 5 day fractionated XRT of the left mandible at 7 Gy per day and were allowed to recover for two weeks. All groups underwent mandibular distractor placement. Groups were distracted at 0.3mm every 12 hrs to a 5.1mm (a critical-sized defect for an irradiated, distracted mandible), and sacrificed on post-operative day (POD) 40. XRT/DO/PTH received 60mg/kg of PTH daily for 3 weeks, starting on POD 4. Coronal sections were obtained and stained using Gomori Trichrome. Statistical analysis was performed with ANOVA and subsequent Tukey or Games-Howell post-hoc tests, dependent on data heterogeneity. Osteoid Volume / Total Volume (OV/TV), Bone Volume / Total Volume (BV/TV), and Osteoid Volume / Bone Volume (OV/TV) ratios were analyzed.

Results: PTH therapy significantly remediated OV/TV, BV/TV, and OV/TV over non-treated, irradiated mandibles (OV/TV: XRT/DO/PTH: 0.75±0.08, XRT/DO: 0.45±0.08, $p<0.01$; BV/TV: XRT/DO/PTH: 0.24±0.08, XRT/DO: 0.54±0.08, $p<0.01$; OV/TV: XRT/DO/PTH: 4.12±3.21, XRT/DO: 0.86±0.28, $p<0.01$), bringing these metrics back to control, non-radiated levels (DO: OV/TV: 0.68±0.12, BV/TV: 0.32±0.12, OV/BV: 2.77±2.32).

Discussion: PTH has been previously shown to remediate radiomorphometrics, vascular analysis, and biomechanical strength in an irradiated model of distraction osteogenesis. Previous research has shown that radiation inhibits osteoid formation and deposition. Low osteoid formation corresponds to hypermineralization and increased fracture and osteoradionecrosis risk. This study quantitatively demonstrated that PTH allows for normal osteoid formation subsequent to a therapeutic dose of radiation therapy, thus potentially deterring these pernicious sequelae of head and neck cancer treatment and reconstruction.

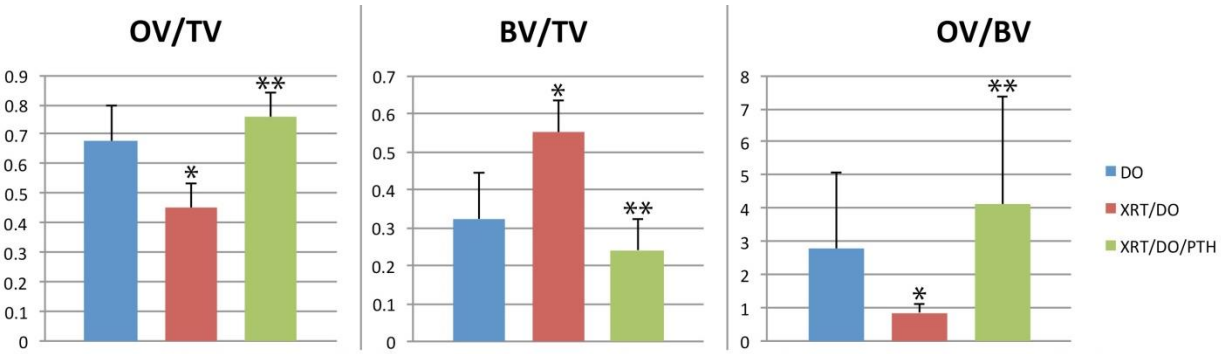

Figure 1. Osteoid Volume / Total Volume (OV/TV), Bone Volume / Total Volume (BV/TV), and Osteoid Volume / Bone Volume (OV/BV) ratios all show significant remediation with PTH therapy. All ratios are unitless. * indicates significance with respect to DO. ** indiciates significance with respect to XRT/DO. *,** indicate $p<0.05$.

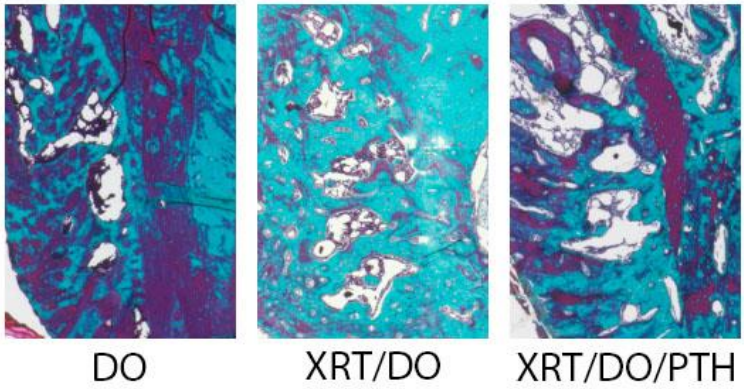

Figure 2. Slide scans of Gomori Trichrome-stained coronal sections demonstrate decreased osteoid volume (red) and increased bone volume (blue) in irradiated sections. Osteoid volume was remediated with PTH therapy.