Adipose Derived Stem Cells Improve Union Rates and Biomechanical Strength Following Fracture in the Irradiated Murine Mandible

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INTRODUCTION: Pathologic fractures and associated non-unions arising in irradiated bone are complex management dilemmas for the reconstructive surgeon. These complications are commonly managed with debridement of necrotic bone and vascularized free tissue transfers. Unfortunately, free tissue transfers remain complex and invasive procedures which are fraught with additional risk and morbidity[1-4]. This study examines a novel treatment paradigm for the management of non-unions and pathologic fractures utilizing implanted adipose derived stem cells (ASCs). Herein, we hypothesize that ASCs will mitigate the detrimental effects of radiation induced injury to the murine mandible and improve clinical union rates and metrics of biomechanical strength.

METHODS: Isogenic Lewis rats (n=36) were divided into 3 groups. Control fracture (n=5), radiated fracture (n=15), radiated fracture + ASCs (n=16). The radiated groups received fractionated, 35Gy (human dose equivalent of 70Gy) radiation over 5 days, two weeks prior to mandibular osteotomy. The radiated fracture + ASCs group received implantation of the ASCs at the time of surgery on a Surgifoam scaffold. Following a 40-day healing period, mandibles were assessed for bony-union and mechanically tested to failure. ANOVA was used for comparison of continuous variables ($p<0.05$) and Chi Square for categorical variables $\chi^2< 0.05$.

RESULTS: *Bony Union*: A statistically significant increase in bony union rates was seen in the radiated fracture + ASCs group (94%) vs radiated fracture alone (20%) $\chi^2=0.00003$. Clinical union rates in the radiated fracture + ASCs group (94%) approximated that of the control fracture group (100%) $\chi^2=0.57$. *Biomechanical Testing*: Significant improvements were found between radiated fracture + ASCs group and radiated fracture group in the metrics of Yield (61.46 N vs 23.5 N, p=0.003), Energy (56.12 Nmm vs 9.97 Nmm p=0.001), and Ultimate Load (73.47 N vs 33.72 N, p=0.002). Additionally, metrics of Yield and Ultimate Load were not statistically different between the radiated fracture + ASCs group and control fracture whereas Energy was significantly improved with ASC treatment (56.12 Nmm vs 9.91 Nmm p=0.001)

CONCLUSION: Our data demonstrate the *in-vivo* efficacy of adipose derived stems cells (ASCs) and their ability to improve clinical union rates and biomechanical properties in the irradiated murine mandible. We support the continued investigation of this novel treatment paradigm and its further translational development for the management of pathologic fractures and associated non-unions after radiotherapy.

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