Effect of External Beam Irradiation on the Pathway of Bone Fracture Healing

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Background/Purpose: External beam irradiation of malignant lesions metastatic to bone has become a widely accepted therapy to prevent fracture and promote bony healing of lesions that compromise the structural integrity of the skeleton. Likewise, following operative treatment of pathologic fractures, external beam irradiation is utilized to accomplish local tumor kill necessary for disease control but potentially interferes with the concurrent need to support fracture healing. We hypothesize that fracture healing by endochondral ossification will be preferentially more impaired than healing by intramembranous ossification in irradiated animals due to radiation-mediated inhibition of the neovascularization and mineralization of cartilage callus during its transition to bone. Therefore, the objective of this study is to investigate the differential effects of radiation on the two pathways of bone healing and propose an optimal method of surgical fracture repair for managing malignant fractures that require external beam irradiation for local tumor control.

Methods: Sprague-Dawley (SD) rats (n = 24; male) were used to develop a bilateral iatrogenic femur fracture model for concurrent study of both healing pathways of bone in the same animal. One side was repaired with a novel, customized dynamically locked intramedullary nail (healing via endochondral ossification) while the other side was rigidly fixed with plate and screws (healing via intramembranous ossification) (Figure 1). On postoperative day 3, the rats in the radiation group (n = 12) underwent radiation treatment using a customized ¼-in-thick lead shield with a small aperture to restrict x-ray exposure to only the fracture sites. The PANTAX x-ray unit was operated at 250 kVp, 13 mA with 1.0-mm aluminum plus 0.5-mm copper added filtration (half value layer 1.56 mm copper) to deliver a single dose of 8 Gy to each femur. In order to study the progression of callus formation, the rats in both control and radiation groups were euthanized at various time points (weeks 1, 2, and 4). The morphology and microstructure of ossification at the fracture site was quantitatively assessed using a Scanco μCT40 system (70 kVp, 114mA and 10 μm isotropic voxel size). Callus volume (CV), bone volume (BV), callus volume fraction (CV/BV), and tissue mineral density (TMD) were determined with a 3-dimensional (3D) volumetric reconstruction technique. A Student t test was used for statistical analysis between control and radiation animals.

Results: A thin layer of calcified callus (Figure 2a, shown in transparent area) gradually formed from week 1 to week 4 around the fracture site in femurs repaired by plate fixation. In the plated femurs, there was no significant difference in the bone volume fraction (CV/BV) of the control group versus radiation group at any of the

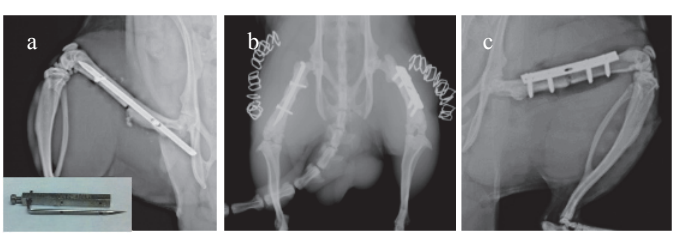


Figure 1. a) Lateral X-ray of IM nail (right femur). b) Anterior-Posterior xray of both femurs. c) Lateral X-ray of plate (left femur).

See pages 47 - 108 for financial disclosure information.

studied time points (Figure 3a). The volumes of calcified callus in the control and radiation groups at week 4 were 22.12 ± 7.49 mm3 and 19.73 ± 5.57 mm3, respectively. By contrast, in femurs repaired by intramedullary (IM) nail fixation, a thicker layer of calcified callus formed around the fracture site (Figure 2b). In the IM nail cohort, a significant difference in the bone volume fraction (CV/BV) was observed between control (39.76 ± 3.50 mm3) and radiation (28.04 ± 7.50 mm3; P <0.005) groups at week 4 (Figure 3b), representing an approximately 40% decrease in bone volume fraction in the radiation group. No statistically significant differences were observed at weeks 1 and 2.

Conclusion: This study suggests a differential effect of radiation on the two pathways of bone healing--an insignificant effect on primary bone healing, or intramembranous ossification, as promoted plate fixation, compared with a significant inhibition of endochondral ossification, or secondary bone healing, as occurs with IM nail fixation. A potential explanation for this may be radiation-mediated inhibition of neovascularization and mineralization of cartilage callus during its transition to bone in the endochondral ossification pathway. In conclusion, internal fixation of malignant metastatic fractures with compression plating, rather than intramedullary devices, may be a more appropriate and durable option for fracture repair of pathologic fractures that require external beam irradiation for local tumor control.

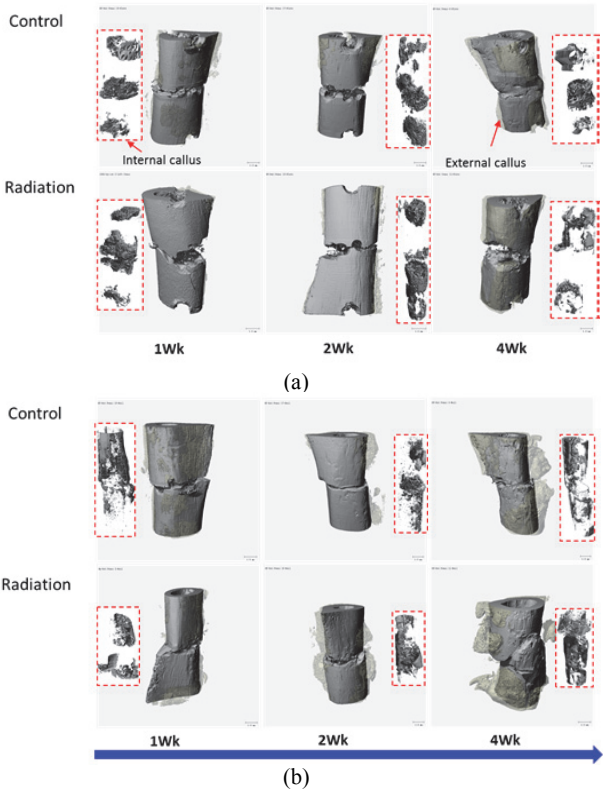
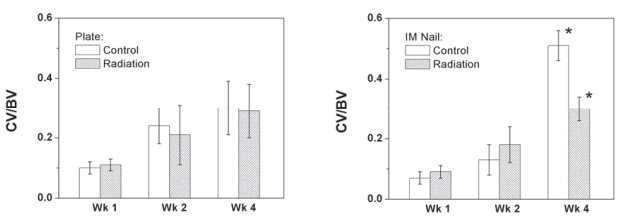


Figure 2. Typical 3D μCT images of external and internal callus formed around the bone fracture site in (a) rat femurs using plate fixation and (b) rat femurs using IM nail fixation at week 1, week 2 and week 4.



(a) (b)

Figure 3. Effects of radiation on the pathways of bone fracture healing in (a) rat femurs using plate fixation and (b) rat femurs using IM nail fixation at various time periods. (*p<0.005, n=6/group at week 4)

The FDA has stated that it is the responsibility of the physician to determine the FDA clearance status of each drug or medical device he or she wishes to use in clinical practice.