**APOTISSONAL BONE GROWTH INHIBITION FOLLOWING IRRADIATION WITH AND WITHOUT RADIOPROTECTANT IN RATS**

*Spadaro, J (A-Departmental Grant); +*Damron, T. A. (A-CMN, OREF, NIH RO1); *Baed, M (A-SUNY Medical Student Stipend); *Conta, A; *Margulies, B (A-CMN, SUNY Intramural Grant); *Strauss, J (A-OREF, SUNY Intramural Grant); **Farnum, C (A-NIH RO1)

+*State University of New York Upstate Medical University, Syracuse, NY. 315-464-4472, Fax: 315-464-6638, damront@upstate.edu

**Introduction:** The treatment of pediatric extremity tumors with radiotherapy may result in shortening and limb deformity when the growth centers are within the radiation field. Appositional growth in width, in comparison to longitudinal growth, has been said to be relatively spared by irradiation (1). While appositional growth in a skeletally mature animal model has been shown to be reduced by irradiation (2), the effect of irradiation on appositional growth relative to longitudinal growth in a skeletally immature animal does not seem to have been reported.

**Purpose:** The purpose was to evaluate the effect of irradiation on appositional bone growth in the skeletally immature rat model as well as the concomitant effect of radioprotectant administration during exposure. The hypothesis was that irradiation affects appositional growth to a lesser degree than longitudinal growth and that radioprotectant use would partially ameliorate this adverse effect.

**Methods:** Forty-eight weanling male 5 week old Sprague-Dawley rats each received a single 17.5 Gy x-irradiation dose to the right distal femur and proximal tibia with the left leg serving as the non-irradiated control. Twelve animals each were euthanized at 2, 4, 6, and 12 weeks after exposure. In each time group, 6 animals received 100 mg/kg of the aminothiol radioprotectant, amifostine, 20 min. prior to irradiation and 6 did not. To determine changes in growth, the hind legs were disarticulated at the hip and the legs radiographed with the tibia and femur in close parallel contact to the film in the lateral view. The tibia and fibula lengths and their widths were then measured from scanned, digitized and calibrated images using NIH Image. The tibial width was measured at sites representing 20%, 30%, and 50% of its length measured from the proximal end, and the fibula width was measured at sites representing 25%, 50%, and 75% of its length, also from the proximal end. Significant differences between irradiated and control legs were inferred using t-tests and accepted at p<0.05.

**Results:** Appositional growth occurred at all measured sites in the tibia, but the response to irradiation was maximal at the proximal third level (30% distal site) and was significantly retarded by radiation exposure at 2, 4, and 6 weeks compared to controls (mean 19-27% reduction, p<0.001). Mean appositional proximal tibial growth with irradiation was 10% less than controls at 12 weeks, approaching significance (p=0.065) [Fig. 1]. Amifostine treatment was associated with reduction of this loss at all time points, reaching significant levels at 2 and 4 weeks compared to irradiation alone (p<0.05).

In the non-irradiated fibula, in contrast to the tibia, the width in the proximal region decreased with growth over time. Maximal width reduction was observed at 12 weeks, reaching on average 40% less than the initial width [Fig. 2]. Irradiation significantly reduced this contraction in width to an average of only 15% less than the initial value (p<0.05). The distal portion of the non-irradiated distal fibula, on the other hand, showed substantial expansion in width (mean 38%, p<0.05) which did not continue after the 4 week period. In irradiated legs, this early distal fibula expansion was clearly reduced (mean 15%, p<0.05 at 2 and 6 weeks), but attained the control width by 12 weeks.

Compared to longitudinal tibial bone growth (3,4), appositional growth in the proximal tibia was reduced by a larger percentage at 2, 4, and 6 weeks after irradiation but by a lower percentage at 12 weeks. Appositional growth appeared to recover over time after irradiation, in contrast to longitudinal growth, where the loss increased over time. Appositional bone growth was reduced most at 4 weeks after irradiation, followed by a tendency to catch up over time to the contralateral control width.

**Discussion:** Based upon these results, appositional growth during skeletal long bone growth does not appear to be spared from the damaging effects of irradiation. In fact, through the time of skeletal maturity in this animal model, appositional growth is affected to a greater extent than is longitudinal growth. However, appositional growth following this dose of irradiation in this animal model does show potential for catch-up over time, unlike longitudinal growth. These differences in susceptibility to the damaging effects of irradiation and potential for recovery are reflective of the differing cell populations affected, eg. the growth plate chondrocytes in longitudinal growth and the periosteal osteoblasts in appositional growth. By contrast, the proximal fibula in this animal model responds in an opposite fashion during normal growth, i.e., with reduction in width, and this reduction was retarded by radiation exposure. In the proximal fibula, we hypothesize that extensive osteoclastic remodeling takes place normally during the rapid phase of longitudinal growth in the Sprague-Dawley rat and that this process is more radiosensitive than appositional bone formation. The radioprotectant aminothiol compound amifostine has some potential to reduce the effects of irradiation on appositional growth.


**Fig. 1:** Width of Irradiated and Non-Irradiated Proximal Tibias vs. Time

**Fig. 2:** Width of Irradiated and Non-Irradiated Proximal Tibias vs. Time

**poster No: 0512**