Effect of P-32 Brachytherapy Bone Cement on Bone Density in an Ovine Model

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INTRODUCTION: Spinal metastases are often treated with vertebral augmentation (VA), i.e. injection of bone cement into the vertebral body, followed by external radiotherapy (RT). We propose to combine VA and RT into one procedure by adding hydroxyapatite powder (HAP) containing P-32 (a β-emitting radionuclide with 14.3 d half-life) to VA cement, thereby creating brachytherapy bone cement to irradiate the bone from within. Potential advantages are delivery of a higher radiation dose to the tumor, minimal dose to the spinal cord and eliminating ~10 radiotherapy visits with unpleasant side effects. In a previous study,[1] we evaluated short-term safety of brachytherapy cement in vivo in ewes. We found no detectable radioactivity from the brachytherapy cement in their blood, urine, or feces and observed no adverse effects. The goal of the present study was to investigate the effect of brachytherapy cement on bone density in the vertebrae of the previous study.

METHODS: Previously, six Rambouillet X Columbia ewes, age 2-3 years, underwent VA in the L-1 or L2 vertebra (after IACUC approval). After drilling a 5.2-mm-diameter hole in the vertebral body, three control ewes received polymethylmethacrylate (PMMA) bone cement mixed with non-radioactive HAP and three experimental ewes received P-32-HAP (2.2, 2.9, and 3.0 mCi/ml). The ewes were euthanized 23 weeks after the procedure and the operative vertebrae were excised. A microCT scan of each vertebra was obtained (Siemens Inveon CT; 0.104-mm slices; ~40-52-micron resolution; 80 kVp; 500 μA; 600 to 900 ms; Feldcamp cone beam convolution kernel). With the cement cylinder viewed along its longitudinal axis (Fig. 1), volumes of trabecular bone surrounding the cement were evaluated in sixteen concentric 0.5-mm-thick shells at 0.5-mm increments, over a distance of 8.0 mm from the cement surface, and over 10 to 23 adjacent images (Siemens Inveon Research Workspace). These 0.5-mm-thick shells, which are identified by their maximum (outer) distance from the cement surface (0.5, 1.0, …, 7.5, 8.0 mm), were divided into quadrants, and the Hounsfield Units (HU) in each quadrant were averaged (HU reflect x-ray attenuation and bone mineral density). Quadrants were excluded if voids in the cement left less than 3 mm of cement adjacent to the quadrant, if cement had leaked into the quadrant or surrounding trabecular bone, or if the quadrant did not include any trabecular bone 8 mm from the cement surface. To account for bone density differences between sheep and variations in cement placement, the mean HU of each shell quadrant was normalized by dividing by the mean HU in the same quadrant 5.0 mm from the cement surface. At a 5-mm distance, the P-32 emissions were not expected to be toxic (estimated lifetime dose, 9.4-13.0 Gy 5.5 mm from the cement surface). For each sheep, the normalized HU (nHU) from shell quadrants with the same outer distance were averaged to obtain the mean nHU within each shell. A 2-way repeated measures (RM) ANOVA (α=0.05) was used to evaluate the effect of P-32-HAP on nHU as a function of shell outer distance, followed by all pairwise multiple comparisons procedures using the Holm-Sidak method with an overall α=0.05 (SigmaPlot for Windows v. 11.0). To address the nonlinear relationship between nHU and distance from the cement, data from the 0.5-mm and 1.0-mm shells were omitted from the 2-way ANOVA, and Student's t-test was used to compare the experimental and control groups.

RESULTS: nHU adjacent to the cement appeared elevated for all animals (Fig. 2). nHU of the radioactive and control groups were not different in the 0.5-mm (p=0.27) and 1.0-mm shells (p=0.87). The 2-way RM ANOVA showed that nHU depended on distance from the cement surface (p<0.001) and revealed an interaction between distance and the presence of radiation (p<0.001). The main effect showed that nHU of the radioactive and control groups did not differ (p=0.4). Within the control group, nHU did not depend on distance from the cement surface (0.1<p<1.0). However, in the radioactive group, nHU within the 1.5, 2.5, 3.0, 3.5, and 4.0-mm shells were respectively greater than nHU of the 4.0, 4.5, 5.5, 6.0 and 7.0-mm shells and beyond (p<0.05). nHU in the radioactive group was greater than that in the control group 1.5 to 3.5-mm from the cement (p<0.04) and less than that in the control group 7.5-mm from the cement (p<0.05). However, these results were likely due to large differences in nHU in two control sheep.

DISCUSSION: The nHU distributions in the radioactive group reflect the bone density distribution after exposure to continuous P-32 irradiation. Previous studies of RT have detected extensive bone resorption within just 4 to 8 months[2,3] so we expected to find reduced bone density, not greater bone density, close to the brachytherapy cement. The lifetime dose 2.3 mm from the cement surface reached an estimated 47 to 65 Gy and increased to above 100 Gy closer to the cement, well above a therapeutic dose for a P-32 implant.[1] The P-32 in this study had mostly (94%) decayed after 8 weeks, leaving 15 weeks for a cellular response. The elevated density immediately adjacent to the cement in the radioactive and control groups may be from creation of the drill hole or from apoptosis of osteocytes and subsequent mineralization of lacunae[4,5] due to toxicity and/or exothermic curing of the PMMA cement. The greater density 2 to 4 mm from the radioactive cement surface is difficult to interpret. Radiation may have caused osteocyte apoptosis and subsequent mineralization of lacunae, followed by continuous P-32 irradiation that prevented osteoclasts from infiltrating and resorbing the irradiated bone. However, without sufficient control specimens with similar bone density distributions, we cannot be sure that the bone density increased in this region. Therefore, we conservatively conclude that P-32 brachytherapy did not cause a detectable decrease in bone density.

This small preliminary study has addressed several key questions and provided important pilot data related to brachytherapy bone cement. Our findings imply that bone may respond differently to continuous brachytherapy from P-32 than to fractionated RT. Future histologic analysis of these vertebrae will provide additional information about the condition of this bone, such as the presence of filled lacunae and the extent of bone remodeling.

SIGNIFICANCE/CLINICAL RELEVANCE: External beam radiation to treat vertebral metastases passes through the spinal cord, which often delays and limits treatment. VA with brachytherapy cement would provide a convenient one-step treatment that spares the spinal cord.

REFERENCES: (1) Keyak JH et al., Phys Med Biol 67:075007, 2022; (2) Santoni et al., Clin Orthop Rel Res, 2008; (3) Wei RL et al., Radiother Oncol, 2016; (4) Busse et al., Aging Cell, 2010; (5) Frost HM, JBJS Am, 1960.

Fig. 1

Fig. 2