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Focused Review

Polymethylmethacrylate and Radioisotopes in Vertebral Augmentation: An Explanation of Underlying Principles

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We recently reported a novel concept for combining radioactive isotope technology with polymethylmethacrylate (PMMA) cement used for vertebral augmentation and have advocated that pain physicians become aware of this new concept when treating malignant compression fractures. The use of vertebral augmentation for malignant compression fractures is steadily increasing, and the goal of this novel approach would be to stabilize the fractured vertebral body while also controlling proliferation of the tumor cells in the vertebral body that caused the vertebral fracture. This approach would therefore provide mechanical stabilization of the fractured vertebral body at the same time as direct targeting of the cancer cells causing the fracture. For our analysis, we investigated six specific radioisotopes with regard to physical and biologic properties as they would interact with PMMA and local bone metastatic disease, taking into consideration anatomical, biological and physical characteristics. The radioisotopes investigated include beta emitting (plus and minus) sources, as well as low energy and mid-energy photon sources and are: P-32, Ho-166, Y-90, I-125, F-18, and Tc-99m.

We review the advantages and disadvantages of each radioisotope. In addition, this paper serves to provide pain physicians with a basic background of the biologic principles (Biologically Effective Dose) and statistical modeling (Monte Carlo method) used in that analysis. We also review the potential complications when using radioactive sources in a clinical setting. Understanding the methodologies employed in determining isotope selection empowers the practitioner by fostering understanding of this presently theoretical treatment option. We believe that embedding radioisotopes in PMMA is merely a first step in the road of local treatment for symptomatic local lesions in the setting of systemic disease.

Key words: polymethylmethacrylate, radioisotopes, vertebral, augmentation, Monte Carlo, biologically, effective, dose

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We recently reported a novel approach for combining a radioactive isotope with polymethylmethacrylate (PMMA) cement used for vertebral augmentation and have advocated that pain physicians become aware of this new concept when treating malignant compression fractures (1,2). The goal of this approach is to stabilize the fractured vertebral body while also controlling proliferation of the tumor cells in the vertebral body that caused the vertebral fracture. While external beam radiation therapy doses to affected vertebral bodies are invariably limited due to the radiation tolerance of the spinal cord and other normal tissues, this technique would provide a localized therapeutic radiation exposure without compromising radiosensitive normal tissues.

Vertebral augmentation is a broad term for a group of minimally invasive procedures which involve the placement of a percutaneous needle into a vertebral body, generally through the pedicle, and the injection of the cement PMMA that is used to augment the vertebral body. A variant of this vertebroplasty technique is kyphoplasty and involves the placement of balloons into the vertebral body in order to create

a cavity, followed by balloon removal and subsequent injection of cement. The PMMA gradually hardens and fills the spaces in the bone (3).

For our analysis, we investigated 6 specific radioisotopes with regard to physical and biologic properties as they would interact with PMMA and local bone metastatic disease. A summary of the radiologic properties of the radioisotopes investigated is shown in Table 1. Assuming a simplistic vertebral phantom in which a small bolus of PMMA mixed with the isotope of interest was placed, we evaluated the radiation exposure rate (absorbed dose) as a function of distance from the bolus. Phantom dosimetry was performed using the MCNP5 Monte Carlo radiation transport code (Los Alamos National Laboratories). This program uses a form of statistical sampling to simulate radiation transport in materials. For clinical purposes, the calculated absorbed dose was converted into the biologically effective dose (BED) for comparison against clinically known radiation therapies. In this report, we review the specifics of the biological properties of the radioisotopes as well as the statistical modeling method that was used to obtain the measurements described.

The Monte Carlo Method

Statistical Sampling is a numerical method which uses randomly generated numbers and probability theory to evaluate integral equations or stochastic based processes. Because "its use of randomness and the repetitive nature of the process are analogous to the activities conducted at a casino" (4), this method was renamed the Monte Carlo technique after a famous casino in Monaco frequented by nuclear weapons physicists in the 1940s. The strength of the Monte Carlo technique is that it provides information on physical systems too intricate to study using deterministic (mathematical) methods and therefore lends itself well towards complex problems in radiation transport and dosimetry. Numerous studies have proven the

Table 1. *Summary of the radiological characteristics for the isotopes studied in this investigation including the advantages and disadvantages of each isotope.*

Radioisotope	T1/2	Decay mode	Advantages	Disadvantages
P-32	14.29d	β-	This pure beta emitting isotope requires a low implant activity and is easy to obtain.	The short range of the beta particle in bone results in a highly localized radiation exposure with a maximum range in bone of ~5mm.
Ho-166	26.8h	β-	Beta source also emits X-ray and gamma radiation including photon energies of ~900 keV. These photons could be used to determine if isotopic leaching occurs.	Dosimetrically, this isotope behaves similarly to P-32
Y-90	64.1h	β-	High energy, pure beta emitter with a greater maximum range than P-32.	While the radiations emitted are more energetic, this isotope still presents a highly localized radiation exposure penetrating only ~6.5 mm in bone.
I-125	59.3d	ε	Low energy photon source provides a more uniform dose deposition to a treatment volume than would a pure beta emitter such as P-32, Y-90.	Due to the high effective atomic number of bone relative to tissue, this isotope could result in excessive bone dose due to higher rate of photoelectric photon absorption in bone for these photons.
F-18	110 m	β+	F-18 typically is used for PET imaging. The positrons emitted by F-18 annihilate with atomic electrons producing two 0.511 MeV photons. These mid-energy photons provide a more uniform dose distribution to a volume than either the low energy I-125 or the pure beta emitting isotopes. The short half-life (110 minutes) results in a short lifetime within the body.	The photons created easily penetrate material. Many photons will be transmitted through the patient. The short half-life will require a local F-18 isotope production source.
Tc-99m	6.01h	IT	Higher energy photon source will have longer effective treatment range than the other isotopes explored in this manuscript; will also have a lower ratio of photoelectric absorption in bone relative to tissue compared to I-125.	Because of the penetrating ability of Tc-99m photons, this isotope would require the greatest amount of activity to be implanted within the patient. Many of these photons will penetrate the patient.

ability of a well written Monte Carlo code to precisely and accurately reproduce experimental results (5).

The MCNP5 Monte Carlo code (6) is a general purpose three dimensional radiation transport program designed to simulate how neutrons, photons, and electrons interact in different materials (5). Specifically, a virtual environment is created within an MCNP program and a radioactive source is defined. A single radiation particle, with characteristics randomly sampled from specifications provided by the user, is created and the distance the radiation travels before interacting within the environment determined. This interaction distance is calculated by comparing published and well known interaction probabilities against random numbers generated by the program; during an interaction, secondary radiations resulting from that interaction are created and similarly transported. The transport process is continued for the primary radiation and all resulting secondary radiations until each radiation either deposits all of its energies within the simulated environment or until it leaves the simulation boundaries. Information on the radiation travel path and energy deposited is maintained, or "scored," by the MCNP program and the simulation process repeated until enough radiation "histories" are run to produce a statistically valid characterization of the radiation path-density (fluence) or energy deposition (dosimetry) in a user selected region or regions of interest.

The MCNP code is capable of simulating photon and electron energies as low as 1 keV and as high as 100 GeV and neutron energies from 10^{-11} MeV to 150 MeV in a wide range of materials (5) and is considered an industry standard radiation simulations code having over 600 person-years of development and maintaining a strong quality assurance and testing program.

The MCNP5 Monte Carlo computer code (version 5.1.4) was used to simulate radiation transport in a 40 mm diameter cortical bone phantom. A 1 mm radial bolus of PMMA, uniformly distributed with one of the six isotopes of interest, was placed at the center of the phantom with dosimetric data computed in a series of 1 mm^3 tally volumes radially distributed out to 1 cm from source center.

The calculated output for both photon and beta emitting sources was multiplied by the isotope's particle yield to obtain the calculated dose deposited in the tally per disintegration, $\dot{D}(r,\theta)$.This result, expressed as the absorbed dose rate per unit activity (cGy μCi^{-1} h^{-1}). The absorbed dose rate per unit activity is directly related to the total absorbed dose per unit activity (cGy μCi^{-1}), assuming an infinite decay period for the isotope, by dividing the absorbed dose rate per unit activity by the decay constant for that isotope.

Biologically Effective Dose

The biologically effective dose (BED) equation, $BED = (nd)(1+d/\alpha/\beta)$, represents a method by which it is possible to compare the probability of tumor control and normal tissue injury associated with the use of different radiotherapy protocols (7,8). In the BED equation, *n* represents the number of fractions and d represents the dose per fraction. The equation takes into account the use of different fraction sizes among protocols. The assumption in the use of the BED equation is that a roughly linear relationship exists between the BED and either the probability for control of the tumor or the development of specific normal tissue toxicity over a particular dose range (9). For either very low or high dose ranges, for which tumor control/normal tissue toxicity levels are either low or high, respectively, the linearity between dose with tumor control probability or normal tissue toxicity may not hold.

The BED, therefore, is equal to the actual physical dose of radiation that is modified by a relative effectiveness factor ($1+d/\alpha/\beta$) that depends upon d and the α/β ratio, which is a characteristic of the particular cancer or normal tissue in the radiation field. Thus, the α/β ratio represents a critical parameter in the BED equation. This value can be derived from isoeffective curves in which a specific radiation-induced effect is produced, such as lung fibrosis, using a series of radiation schedules employing different sized fractions (10). Generally, the smaller the size of the dose fraction employed, the greater will be the dose needed to produce the effect of interest. This is usually observed because use the smaller the dose utilized, the greater is the chance that the radiation damage can be repaired between dose fractions and therefore not elicit the normal tissue complication or provide the desired level of tumor control.

If fraction size plays a large role, then the α/β as computed from the isoeffective curve will be a low value. Therefore, changing a radiotherapy protocol from use of many small dose fractions to one with a small number of large fractions will have a great impact on the BED. Conversely, if the α/β calculated from an isoeffective curve analysis is high, then changing the dose per fraction will have only a small impact and only the total dose will exert the main affect on the BED.

It should also be noted that often the critical normal tissue in the radiation field that limits the size of the dose that can be delivered exhibits a smaller α/β than the cancer being treated. In these instances, it would be advantageous to use a protocol in which the total radiation dose is delivered in a large number of treatments (25-30) each employing a small dose per fraction (1.1-2.0 *Gy*). However, for certain malignancies, such as prostate cancer, the reverse may be true and provide a basis for the use of large fraction sizes (11,12). In other instances, such as breast cancer, there is evidence that the α/β ratios may be similar for the tumor and surrounding normal tissues, which then permit flexibility in the size of fractions used (13,14).

The basic BED equation does not take into account dosimetric parameters which will have an impact on tumor control and normal tissue effects. In particular, a more conformal treatment in which the normal tissues are spared and exposed to a reduced amount of radiation will decrease the BED (15). Table 1 presents a comparison of advantages and disadvantages of the isotopes studied. This comparison was based on the Monte Carlo results and BED calculations.

Potential Complications

In addition to the potential procedural risks associated with vertebral augmentation and any minimally invasive procedure, including bleeding and infection, there are certain risks inherent to the radiobiologic properties of the radioisotopes. Risks of use of radioisotopes include excessive radiation dose to the cortical bone and other normal tissues near the augmented vertebral body as well as leaching of the radioisotope from the PMMA cement leading to systemic radioisotope dissemination and radiation uptake in radiosensitive tissues and organs. Preliminary analysis of the leaching properties of each radioisotope in relation to the PMMA cement is currently under investigation.

Conclusion

We believe that embedding radioisotopes in PMMA is merely a first step along the road of local treatment for local symptom control in a systemic disease. Malignant compression fractures are on the cutting edge of that change. Understanding the methodologies employed in determining isotope selection empowers the practitioner by fostering understanding of this presently theoretical treatment option. The goal of this approach is to stabilize fractures in vertebral bodies and to control the tumor cell population causing these compression fractions.

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References

1. Hirsch AE, Medich DC, Rosenstein BS, Martel CB, Hirsch JA. Radioisotopes and vertebral augmentation: Dosimetric analysis of a novel approach for the treatment of malignant compression fractures. *Radiother Oncol* 2008; 87:119-126.
2. Hirsch AE, Hirsch JA. The evolving management of malignant compression fractures. *Pain Physician* 2008; 11:699-700.
3. Jha RM, Yoo AJ, Hirsch AE, Growney M, Hirsch JA. Predictors of successful palliation of compression fractures with vertebral augmentation: Single-center experience of 525 cases. *J Vasc Interv Radiol* 2009; 20:760-768.
4. Metropolis N. The Begining of the MONTE CARLO Method. *Los Alamos Science* 1987;Special Issue(1987):125-130.
5. Briesmeister JF. *MCNP - A General Monte Carlo N-Particle Transport Code, Version 4C.* Los Alamos: Los Alamos National Laboratory; April 2000. LA-13709-M.
6. Booth TE, Brown FB, Bull JS, Cox LJ, Forster R., Goorley JT, Hughes HG, Mosteller RD, Post SE, Prael RE, Selcow EC, Sood A. *MCNP - A General Monte Carlo N-Par ticle Transport Code, Version 5*. Los Alamos: Los Alamos National Laboratory; April 2003. LA-UR-03-1987.
7. Thames HD, Jr., Withers HR, Peters LJ, Fletcher GH. Changes in early and late radiation responses with altered dose fractionation: implications for dose-survival relationships. *Int J Radiat Oncol Biol Phys* 1982; 8:219-226.
8. Barendsen GW. Dose fractionation, dose rate and iso-effect relationships

for normal tissue responses. *Int J Radiat Oncol Biol Phys* 1982; 8:1981-1997.

9. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. *Br J Radiol* 1989; 62:679-694.
10. Douglas BG, Fowler JF. The effect of multiple small doses of x rays on skin reactions in the mouse and a basic interpretation. *Radiat Res* 1976; 66:401-426.
11. Ritter M, Forman J, Kupelian P, Lawton C, Petereit D. Hypofractionation for prostate cancer. *Cancer J* 2009; 15:1-6.
12. Fowler JF. Biological factors influencing optimum fractionation in radiation therapy. *Acta Oncol* 2001; 40:712-717.
13. Bentzen SM, Agrawal RK, Aird EG, et al. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008; 9:331-341.
14. START Trialists' Group, Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bentzen SM, Bliss JM, Brown J, Dewar JA, Dobbs HJ, Haviland JS, Hoskin PJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Morgan DA, Owen JR, Simmons S, Sumo G, Sydenham MA, Venables K, Yarnold JR.The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008; 371:1098-1107.
15. Jani AB, Hand CM, Lujan AE, Roeske JC, Zagaja GP, Vijayakumar S, Pelizzari CA. Biological effective dose for comparison and combination of external beam and low-dose rate interstitial brachytherapy prostate cancer treatment plans. *Med Dosim* 2004; 29:42-48.