Design of practical proton-activated implantable markers for proton range verification using PET

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Specific Aims: The aim of this research project is to develop a fiducial marker that can be used for in vivo proton range verification following proton therapy. Our group has previously shown the feasibility of using novel elements as proton-activated fiducial markers that can be imaged using an off-site PET scanner (Cho et al 2013). In this research, we will investigate the optimal physical configuration of those markers while ensuring their detectability in a PET imaging and minimizing their physical size to allow their implantation in many human organs. In this regard, we intend to develop a fiducial marker that (1) is easy to implant, (2) does not migrate, and (3) provide adequate radio-opacity and (4) is detectable in PET images after irradiation by protons. The developed fiducial markers will serve as normal radiographic/CT fiducial markers and provide additional information for proton range and therapy verifications using PET.

Specific Aim I: Determine the optimal dimension/diameter of Cu and 65Zn foils/wires that give the maximum PET signal strength per volume. Specific Aim II: Find the optimal volume of markers that provide adequate PET signals. Specific Aim III: Determine the shape of markers using the determined optimal volume that provide optimal PET signals.

Background: The main advantage of proton therapy is evident in the Bragg peak, which shows that proton beams deposit their maximum dose near the end of the proton range, with little or no dose beyond that point. This advantage, however, requires precise estimation of the exact proton range; otherwise, underdosage of the target or overdosage of distal critical organs can result. Although estimates of proton range uncertainty have varied depending on the investigator (Mustafa and Jackson 1983, Alpen et al 1985, Moyers et al 2010, Paganetti 2012), a 3.5% range uncertainty is most widely accepted in current x-ray CT-based planning practice. This degree of uncertainty, however, translates to a misestimation of the proton range as large as 2 cm in the lung for thoracic treatments.

Because of this uncertainty, most current proton treatment plans do not use beam configurations which position critical organs distal to the target. For example, patched field arrangements offer a compromise between non-uniform target dose delivery and critical organ sparing by avoiding the beam direction towards critical organs (Lomax et al 2001). Alternatively, proton beams with longer than optimal ranges and wider than optimal modulation widths may be prescribed to ensure full dose coverage of the target (Paganetti 2012b). These practices come at a cost, however, as they result in less than ideal treatment beam configurations and increased normal tissue irradiation.

Uncertainty in proton range estimation has been the driving force for various studies of in vivo proton range verification. Several investigators (Paans and Schippers 1993, Oelfke et al 1996, Nishio et al 2005, Crespo et al 2006, Parodi et al 2007a, 2007b, Knopf et al 2008, Nishio et al 2008) have suggested the use of proton tissue activation followed by positron emissions for proton range verification; this is currently the only clinically used approach. Proton-induced PET imaging has several fundamental limitations: minimal activation of tissues near the proton range (Litzenberg et al 1999), activity washout (Mizuno et al 2003, Tomitani et al 2003, Parodi et al 2007b, Knopf et al 2009), and short half-lives of activated tissues. Additionally, such an approach would require an on-site and preferably in-room PET scanner, which could be a financial burden for many proton centers (Shakirin et al., 2011, Min et al., 2013).

To overcome these challenges, we have previously (Cho et al 2013) suggested the use of implantable fiducial-like markers for in vivo proton range verification. When irradiated with protons, these markers are strongly activated and decay mostly by positron emissions with relatively long half-lives. Therefore, the suggested method can take advantage of off-site PET scanners and is more financially viable for many proton centers. The idea of implanting a dosimeter for time-resolved proton range verification has been suggested by
signals for using more clinically relevant dose with use of an activation for proton range verification compared to acquired for 30 min with a 50 min post-irradiation delay. All irradiated markers were strongly activated at the end of the proton beam range. In addition, the radioisotopes created by proton interaction decay with relatively long half-lives. These markers are also free of signal reduction due to activity washout.

**Preliminary Results:** We identified two materials as candidates for proton range verification markers: $^{63}$Cu and $^{68}$Zn. They have large proton nuclear interaction cross-sections ranging from several hundred to more than 1000 mb (EXFOR library), which is about 10 times greater than those of endogenous tissue elements (figure 1). Furthermore, their interaction energy thresholds are only a few MeV (which equates to a sub-millimeter proton residual range), which could potentially allow PET imaging to determine the end of the proton beam range. In addition, the radioisotopes created by proton interaction decay with relatively long half-lives. Therefore, when implanted in the target volume, these materials could potentially be used to verify the proton beam range with an off-site PET scanner (Cho et al. 2013).

Natural Cu foils were used due to its high $^{63}$Cu (>69%) enrichment and 98% enriched $^{68}$Zn foils (Trace Sciences International, Richmond Hill, Ontario, Canada) were used for experiments. Two types of markers (50 mm $^3$ Cu and $^{68}$Zn markers) were made by stacking five 10 × 10 × 0.1 mm $^3$ Cu or $^{68}$Zn foils. Those markers were embedded in a high density ($\rho = 0.3$ g/cm$^3$) balsa wood phantom whose activation resembles unit density soft-tissue (figure 2(a)). A passively scattered SOBP proton beam was irradiated from below so that depths 1 – 4 are located over the distal dose fall-off region (figure 2(b)).

Figure 3(a) – (f) shows PET/CT fusion images of the activated balsa wood phantom. PET images were acquired for 30 min with a 50 min post-irradiation delay. All irradiated markers were strongly activated compared with the background from the activated balsa wood phantom. The relatively weaker activation of Cu at depth 4 indicated the distal end of Cu activation. Figure 3(e) and (f) shows the feasibility of using marker activation for proton range verification; phantom activation alone cannot accurately estimate this range since its signal starts to decrease at a significantly shallower depth. The experiment in figures 2 and 3 was performed with use of a relatively large dose (12.5 Gy) and marker volume (50 mm$^3$), although the typical treatment dose and marker volume are 2 Gy and 10 mm$^3$, respectively. Therefore, characterization studies were performed by using more clinically relevant doses (1, 2, 3, 4 and 5 Gy) and marker volumes embedded in more tissue-like phantoms.

The purpose of these studies was to determine Cu and $^{68}$Zn marker volumes that give acceptable PET signals for various doses, phantoms and PET scan times. Markers of various area sizes (10×10 and 5×5 mm)
and thicknesses (0.1, 0.2, 0.4, and 0.5 mm) making up various marker volumes (10, 20, and 50 mm³) were embedded in low density (ρ ~ 0.1 g/cm³) balsa wood as a lung-tissue replacement and also in blocks of beef (ρ ~ 1.0 g/cm³) as a soft-tissue replacement. Figure 4 shows a few examples of PET/CT fusion images of some markers embedded in balsa wood and irradiated by various doses. A total of 13 radiologists scored the activation of various markers with a 5-pont scale visibility score (eg, 1 – not visible, 3 – moderately visible and 5 – strongly visible). Regression study was performed to determine the required volume for 10×10 mm sized markers to give moderate PET signals (visibility score of 3).

Table 1 shows the required volume of 10×10 mm sized markers that gives acceptable PET signals (or
visibility score) relative to the background phantom signals. Figure 5 shows a surface plot of the visibility score of 10×10 mm sized Cu markers with marker volume and dose. As the marker volume and dose increase, the visibility increases. When the area size of the marker was 10×10 mm, 4~55 mm³ of volumes (or 0.04~0.55 mm in thicknesses) were required to provide the acceptable visibility score (table 1). Therefore, the visibilities of smaller area size (5×5 mm) markers were investigated for different marker thicknesses. Previously it was observed that the increase of marker surface size (from 5×5 mm to 10×10 mm) increased the marker visibility, however, the increase of marker thickness increased the visibility more significantly. For example, drastic marker visibility differences were observed amongst the same volume of 10 mm³ ⁶⁸Zn markers in figure 4(a), (b) and (c). Although 5×5 mm markers (thickness of 0.4 mm) were irradiated by lower doses – 4 Gy for figure 4(b) and 2 Gy for figure 4(c), they show greater visibilities compared to 10×10 mm markers (thickness of 0.1 mm) which has the same volume and were irradiated by even higher dose – 5 Gy.

| Table 1. Required marker volume (mm³) to obtain acceptable PET signals (visibility score of 3) for 10×10 mm sized Cu and ⁶⁸Zn markers embedded in a beef phantom (unpublished data). |
| Scan time | Cu markers | ¹⁹⁷⁶⁸Cu markers |
| 1 Gy | 2 Gy | 3 Gy | 4 Gy | 5 Gy | 1 Gy | 2 Gy | 3 Gy | 4 Gy | 5 Gy |
| 20 min | 55 | 49 | 42 | 36 | 30 | 35 | 29 | 23 | 16 | 10 |
| 30 min | 52 | 45 | 39 | 33 | 27 | 32 | 26 | 20 | 13 | 7 |
| 40 min | 49 | 42 | 36 | 30 | 24 | 29 | 23 | 17 | 10 | 4 |

This example shows that increases in marker thickness contribute towards the marker visibility more significantly than the marker surface area increase. We speculate that the reason for the higher visibility of the 5×5×0.4 mm markers is due to high median kinetic energies (~1 MeV) of positrons created by Cu and ⁶⁸Zn activations. A large number of positrons created in the thinner markers (10×10×0.1 mm) could have escaped from the markers and result in lower PET signals (Cho et al. 2013). Figure 4(b) and (c) shows how those markers can be made small (~10 mm³) and still provide acceptable PET signals even when irradiated by lower dose. Interestingly, increasing the marker thickness beyond a certain value resulted in lower PET signals per marker volume. For example, Cu beads with 2-mm diameters, Cu cylinders with 2-mm diameters and 2-mm lengths, and 0.4 mm thick flat Cu markers were located at the proton distal fall-off region and irradiated using a 10 cm SOBP proton beam (160 MeV). **PET signal strengths per marker volumes were significantly lower for Cu beads and cylinders than flat Cu markers.** Similarly, Cu wires of various diameters (0.3 ~ 1 mm) were irradiated. Wires with smaller diameters produced significantly greater PET signals per volume than wires with greater diameters. We suspect that thick markers did not provide a strong PET signal as did thin markers because protons rapidly lose their energy while penetrating the thick volume of markers. Protons failed to activate the entire volume of Cu beads, cylinders, and thick wires (1~2 mm) but did uniformly activate the much thinner Cu markers and wires (0.3 ~ 0.4 mm). For this reason, it is crucial to study the design of implanted marker geometry.

**Research Plan:**

**Specific Aim 1:** *Determine the optimal dimension/diameter of Cu and ⁶⁸Zn foils/wires that give the maximum PET signal strength per volume.* This will be accomplished by determining the optimal area and thickness combination of Cu and ⁶⁸Zn foils that give the maximum PET signal strength per foil volume for foils of different combinations of surface size (5×5 mm or less) and thickness (0.8 mm or less). Also 10 mm long Cu
and $^{68}$Zn wires of different diameters (0.1 ~ 0.8 mm) will be used to determine the diameter that gives the maximum PET signal strength per wire volume. Foils and wires will be embedded in two tissue-like phantoms (balsa wood and beef) and CT scanned. Treatment plan will be performed to position the foils and wires at the proton distal fall-off region. Dose of 2 Gy will be delivered and phantoms will be moved to an off-site PET scanner and imaged. 30 min PET acquisition time with various post-irradiation will be used to obtain the maximum SNR for foils/wires relative to background phantom signals. Monte Carlo simulation will be utilized to study the change of PET signals for the entire spectrum of size and thickness combinations. Activation followed by PET measurements will be performed for a selected size and thickness combinations. We previously performed specific aim I measurements for a few sets of combinations successfully. We do not anticipate any difficulty in completing specific aim I measurements for the complete set of combinations.

**Specific Aim II:** Find the optimal volume of markers that provide adequate PET/CT signals. This will be accomplished as follows. From the determined optimal dimension/diameter from specific aim I, we will determine the optimal numbers of foils and wires which give adequate PET/CT signals for various dose (1 ~ 5 Gy) and PET scan time (20 ~ 40 min). The optimal volumes of foils and wires are determined from those optimal numbers (volume of each foil or wire × number of foil or wire). A similar characterization study performed to create table 1 will be repeated here.

**Specific Aim III:** Determine the shape of markers using the determined optimal volume that provide optimal PET/CT signals. The designs of two commercially available fiducial markers (VISICOIL™ in figure 6 and Gold Anchor™ in figure 7) provide some insight for our marker design. Although both markers use very thin gold wires (0.1 ~ 0.2 mm diameter), when coiled or collapsed they provide adequate radio-opacity for use in radiographic fiducial markers. Specific aim III will be accomplished as follows. Thin foils will be rolled (like cinnamon rolls) into a cylinder using the section (parallel to the cylinder axis) area and accumulated foil thickness (when penetrating through the entire foils) equal to the area and thickness determined from specific aim I. The length of the cylinder will be decided from the optimal volume of markers determined from specific aim II. Similarly, wires of the optimal diameter will be coiled or collapsed like figures 6 and 7. Similarly wires of half the optimal diameter will be coiled or collapsed. The lengths of the wires will be determined from the optimal volume of wire found in specific aim II. Monte Carlo simulation will be used to find the best geometry that satisfies the following conditions: (1) small size, (2) maximum PET signals, and (3) easy of implantation.

**Future studies:** If the size of the rolled cylinder found in specific aim II is small, it can be implanted using a needle. However, it is too large, we plan to construct a spring-type wire or notched thin wire that can be inserted and kept straight in a fiducial inserting needle. Once implanted (or pushed out of the needle), however, this wire will be programmed to collapse into a coil or a 3-dimensional shape as figure 7. The markers we develop will be tested in tissue-like phantoms (balsa wood and beef) representing two tissue types – lung and soft tissue. Although the following is beyond the scope of the proposed research, once the proposed and AAPM sponsored research is completed, animal studies can be conducted using a larger grant by implanting markers into relatively large animals such as pigs. I am planning to apply for other seed grants and trainee grants to allow further studies. First clinical studies can be performed in the prostate. Markers can be carefully positioned in the rectum using a rectal balloon. After proton treatment, patients can be moved to an off-site PET scanner for imaging and proton range verification.
Literature Cited:


Moyers MF, Sardesai M, Sun S and Miller D 2010 Ion stopping powers and CT numbers Med. Dosim. 35 179–94

Nishio T, Sato T, Kitamura H, Murakami K and Ogino T 2005 Distributions of β+ decayed nuclei generated in the CH$_2$ and H$_2$O targets by the target nuclear fragment reaction using therapeutic MONO and SOBP proton beam Med. Phys. 32 1070–82


Budget:

<table>
<thead>
<tr>
<th>Purchase and expense items</th>
<th>Cost</th>
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</thead>
<tbody>
<tr>
<td>$^{68}$Zn foil cost: $300 per 10 mm × 10 mm × 0.1 mm foil (97.8±0.2% $^{68}$Zn enrichment, Trace Sciences International, Richmond Hill, Ontario, Canada; density = 7.14±0.50 g/cm³), Required number of foils: 10, total cost: $500 × 10 =</td>
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<td>98% enriched $^{68}$Zn wire cost: $600 per 10 cm wire (0.8 mm diameter) Required number of wires: 10, total cost: $600 × 10 =</td>
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<td>Copper foils and wires</td>
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<td>Multiple balsa wood phantoms</td>
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**Principal mentors and collaborators:**

Dr. Geoffrey Ibbott, professor and chair in the Department of Radiation Physics, and Dr. Osama Mawlawi, professor and section chief of Nuclear Medicine in the Department of Imaging Physics at MD Anderson Cancer Center, Houston, TX.

Dr. Eric Ford, assistant professor in the Department of Radiation Oncology at University of Washington, Seattle, WA.