Study of the Angular Dependence of a Prompt Gamma Detector Response during Proton Radiation Therapy

Eunsin Lee, PhD1; Jerimy C. Polf, PhD2; Dennis S. Mackin, PhD3; Sam Beddar, PhD3; Derek Dolney, PhD4; Christopher Ainsley, PhD4; Ali Kassaee, PhD4; Stephen Avery, PhD4

1Department of Radiation Oncology, University of Washington, Seattle, WA, USA
2Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, MD, USA
3Department of Radiation Physics, University of Texas MD Anderson Cancer Center, Houston, TX, USA
4Department of Radiation Oncology, University of Pennsylvania, Philadelphia, PA, USA

Abstract

Purpose: Several studies have recently shown that the characteristics of prompt gamma (PG) rays emitted during proton radiation therapy are beneficial for verifying proton beam range during treatment delivery. Since PG rays are produced instantaneously upon the proton beam delivery, the viability of in vivo beam range verification using PG rays depends greatly on the design optimization of not only intrinsically highly efficient detectors, but also detector location around the beam to maximize detection efficiency. The purpose of this study is to characterize angular dependence of the PG detection rates as a function of proton beam energy to help develop the design of clinically feasible detectors.

Materials and Methods: In this study as a part of the long-term goal of developing a clinically feasible multistage Compton camera, we performed a Monte Carlo–based study of the detector response in a water phantom over the clinical range of beam energies, 50 to 200 MeV, and characterized PG emission spectra at various angular (azimuthal as well as polar) positions to optimize the detector location to get the maximum detection rate. We also performed a similar study by using the computed tomography data set for a prostate case and using a representative double-scattered treatment beam.

Results: Regardless of beam energy, the total PG ($2.3 \times 10^{-2}$ at $\theta = 45^\circ$ to $4.6 \times 10^{-2}$ at $\theta = -45^\circ$) as well as $^{16}$O gamma detection rate ($3.5 \times 10^{-4}$ at $\theta = 45^\circ$ to $5.6 \times 10^{-4}$ at $\theta = -45^\circ$) was higher at locations proximal to the proton treatment nozzle, with no significant dependence on the azimuthal angular rotation of the detector around the beam axis. Furthermore, as the proton beam energy increased, the detection rate for both the total gamma rays and $^{16}$O emission increased, while the relative production of PG rays from the $^{16}$O elemental line decreased.

Conclusion: We expect that the spectral and spatial characteristics of PG emission from a proton-irradiated target shown in this study will help design and optimize a PG detector system to maximize detection efficiency, with an appropriate choice for the number of detector nodes and their corresponding angular positions around the proton beam, taking into account geometric constraints in the treatment room.

Keywords: proton therapy; range verification; prompt gamma imaging
Introduction

In radiation therapy, the goal is to deliver sufficient dose to ensure local tumor control while simultaneously limiting the dose to healthy organs to avoid radiation damage. Even though x-rays have shown great success in treating cancer, the challenge in using high-energy x-rays is that the x-rays deposit an entrance and an exit dose to healthy organs as they pass through the body: the dose to healthy organs limits the dose to the tumor. Proton beam therapy potentially provides an improved dose distribution because of the steep distal falloff at the end of the proton beam range with sharp maximum dose deposition, known as the Bragg peak. However, for this advantage to be fully exploited, the location of the sharp distal gradient in the patient must be precisely controlled. Range uncertainties come from many sources including errors in patient setup or positioning, variations in patient anatomy including the size of the tumor, and limitations of the dose calculation algorithm. The process by which x-ray computed tomography (CT) numbers are converted to proton stopping powers in treatment-planning systems can lead to large range estimation uncertainties, up to 10% in extreme cases, owing to heterogeneities and the presence of anatomic structures with high atomic numbers, such as bone, along the beam path [1, 2]. Uncertainties in the dose delivery require that adequate safety margins be built into each patient treatment plan to ensure target coverage, at the cost of additional dose to healthy tissue, and furthermore the effect of range errors on dose to nearby critical organs must be considered carefully [3]. Therefore, to reduce necessary margins and to fully benefit from the advantages of proton beam therapy, a means of in vivo dose monitoring during tumor irradiation is needed to verify the dose distribution in and around the target volume.

Proposed methods for in vivo proton beam range verification revolve around the measurement of the secondary gamma rays emitted from the irradiated patient during the treatment. One such method is in-beam positron emission tomography (PET), which relies on the creation of positron-emitting isotopes (¹¹C, ¹⁵O, etc) that produce coincident, 511-keV annihilation gamma rays [4–10]. However, the geometric restriction of a conventional whole-body PET scanner limits its installation in the treatment room, and a dual-head PET camera [11–13] or a partial-ring PET scanner [14] collects incomplete data samples, producing image artifacts due to limited angular coverage [15].

Another possible method for beam range verification involves the measurement of prompt gamma (PG) rays. Inelastic collisions of incident protons and target nuclei produce characteristic PG ray emission following the decay of excited nuclei to their ground state. Recent investigations [16–19] have shown that the longitudinal distribution of the PG emission is correlated with the proton dose profile in the distal falloff region. This provides a rationale for the use of the PG signal for in vivo verification of the proton dose delivery and range.

However, owing to the preponderance of relatively high-energy gamma rays (2–15 MeV), the detection efficiency of standard gamma camera detectors using a 2-dimensional collimator is not adequate for the imaging of PG emission during proton beam irradiation [20]. Therefore, to measure the energy and spatial characteristics required for a clinically viable imaging system without relying on traditional 2-dimensional collimation or total absorption of the gamma rays, the Compton camera has been investigated as a possible method by several research groups [21–23].

Compton cameras are multistage (2 or 3 stages) detectors that measure the initial energy and direction of Compton scattered gamma rays in each stage of the detector.
Recently, several Monte Carlo (MC) studies of a multistage Compton camera have been completed to optimize geometric design parameters [24], to identify the most suitable detector materials [25], and to evaluate a stochastic image reconstruction algorithm [26] for the measurement of PG rays emitted during proton therapy.

While those studies provided a theoretical framework for the clinical use of the Compton camera imaging as a patient proton beam range verification device, further study of the spectral and spatial characteristics of PG emission from a proton-irradiated target is needed to design and optimize a PG detector system, to maximize detection efficiency with an appropriate choice for the number of detector nodes and their corresponding angular positions around the proton beam, taking into account geometric constraints in the treatment room.

Figure 1A shows a Compton camera imaging system with 3 detector stages. The kinematics of the Compton scattering process uses the energy deposition and position for each scattered gamma to determine the PG's incident energy and the angle of its initial scatter in the detector [27]. Figure 1B shows preliminary MC results of a PG image reconstructed by using the triple-stage Compton camera. From the previous studies [24, 25], we used 3-stage Compton camera composed of high-purity germanium (HPGe) and incorporated it into our MC model of the University of Pennsylvania proton nozzle system.

Our goal in this work was to investigate the angular dependence of the detector response to PG emission during proton therapy. Specifically, using MC simulations, we first evaluated the impact of various angular positions of a detector on the detection rate of the characteristic PG spectra for a range of proton beam energies in both a water phantom and a CT data set from a patient with prostate cancer. Quantifying the relative detection rates at different angular positions is necessary, since analyzing PG emissions along the entire proton beam path in the target can provide not only the delivered dose distribution for a given fraction, but also the information of changes in the composition of irradiated tissues, such as anatomic changes and/or changes in the level of tumor hypoxia during the course of treatment [17, 28].

In particular, $^{16}$O is one of the most abundant nuclides in human tissue, and the 6.13-MeV gamma emission line from $^{16}$O that results from the $^{16}$O(p, p')$^{16}$O$^*$ reaction has been...
shown to have a particularly strong correlation with the proton dose deposition [29, 30]. Figure 2 shows the MC-calculated dose deposition profile, total PG emission, and $^{16}$O gamma emission in the patient CT data set irradiated with a double-scattered proton beam at the University of Pennsylvania. The 1-dimensional plot of these profiles showed a strong correlation between proton dose profile, total PG emission, and $^{16}$O gamma emission. The distal falloff of the $^{16}$O gamma emission was well matched to the distal falloff of the proton dose deposition, whereas the total PG emission had significant components in both the entrance and plateau regions before the Bragg peak. In addition, the peak of the total PG emission occurred approximately 2 cm before the Bragg peak owing to higher PG signal from inhomogeneous anatomic structures such as bone, muscle, and other tissues.

Therefore, we also analyzed both the 6.13-MeV gamma emission yield from $^{16}$O and the total PG production inside the water phantom and the patient for various proton beam energies. Finally, we quantified both the PG and $^{16}$O gamma detection rates, and the fraction of $^{16}$O gamma production relative to total PG rays from the water phantom as well as the patient, as a function of angular position of the detector and proton beam energy.

**Materials and Methods**

**Simulation Setup**

For the MC modeling, we used the simulation package developed at the University of Pennsylvania for an Ion Beam Applications (IBA) double-scattering proton therapy nozzle (Ion Beam Applications, SA, Louvain-la-Neuve, Belgium) and a Varian MLC (2009; Varian Medical Systems, Palo Alto, CA, United States) using the GEANT4.9.4 toolkit [31]. Our physics list, originally provided by Jarlskog and Paganetti [32], was modified for the newer version of GEANT4 by replacing G4MultipleScattering with G4eMultipleScattering for electrons and positrons and with G4hMultipleScattering for hadrons. Our model of the nozzle included a realistic implementation of the modulator wheels, first and second scatterers, and MLC (Multileaf Collimator) and patient-specific compensators; the model reproduced commissioning data to within 2-mm range accuracy and 1% dose accuracy.
Since previous studies [25] have shown that a single-material germanium detector has the highest single-material efficiency among other materials studied, for the purposes of this study, we also decided to incorporate a cylindrical HPGe detector to simulate PG detection by scoring fluence within a validated MC model [18]. Figure 3A shows a schematic diagram of the MC-modeled IBA beam nozzle with the HPGe detector. We used the G4EmLivermorePhysics model to calculate electromagnetic and gamma interactions in the HPGe detector. A maximum step size of 1 mm was set for all particles tracked in all geometry elements in the model. A particle range cut of 0.5 mm was set for gamma, electron, positron, and proton, which means that secondary particles with ranges below this threshold were not produced; instead, the remaining particle energy was deposited over the length of the final step.

The modeled geometry of the HPGe detector had a radius of 10 cm and a length of 7 cm, with a Compton suppression shielding system including an inner cylinder of a bismuth-germanium-oxide crystal and an outer cylinder of lead shielding. Only gamma rays that interacted in the HPGe detector but not in any of the shielding parts were recorded. The

Figure 3. (A) Schematic diagram of the Ion Beam Applications IBA proton therapy beam nozzles with Varian MLC at the University of Pennsylvania and the cylindrical HPGe detector placed perpendicular to the 10 cm × 10 cm × 50 cm water phantom. Also shown is the detector position and orientation for various (B) polar and (C) azimuthal detector angles. The proton beam direction was chosen as the positive z-direction. Polar angles of 45° (far from the nozzle-forward), 0° (perpendicular to the beam direction), and –45° (near the nozzle-backward) were studied. Azimuthal angular positions around the beam axis of 0°, 45°, 90°, 135°, and 180° with respect to the positive x-axis were studied. Abbreviations: HPGe, high-purity germanium; MLC, Multileaf Collimator.
detector was located 30 cm from the beam central axis. For a more detailed description of the HPGe geometry, see the study by Polf et al [18].

A homogeneous water phantom and a CT data set from a patient with prostate cancer were implemented into the simulation as the volumes to be irradiated during proton beam treatment delivery. The water phantom had a 10 cm × 10 cm cross-section in the x-y plane, was centered perpendicular to the beam, and was of variable length along the beam direction chosen according to the beam energy, such that the Bragg peak was located at its center in each case.

The patient CT data set consisted of 293 CT slices (512 pixels × 512 pixels, 1.5 mm thick, 50-cm field of view) and was incorporated into the MC model to study PG emission during delivery of treatment to a real patient. A voxelized patient geometry was constructed in GEANT4 by using the G4PhantomParameterisation class and a voxel size corresponding to that of the patient CT data set. The material for each voxel was assigned by following the GEANT4 extended/medical/DICOM example, which divides the Hounsfield unit range into 10 bins with chemical composition corresponding to patient tissues. However, the material density was not binned as in the GEANT4 example; instead, a unique density for each Hounsfield unit value was used as discussed [33].

Parameters Studied and Data Analysis

To characterize the dependence of the HPGe detector’s response on the angular distribution of PG emissions, we placed the HPGe detector at various angular locations as shown in Figure 3B and 3C. In the polar angle (as measured from the beam central axis [z-axis]), we placed the detector at 45° (away from the nozzle), 0° (perpendicular to the beam line), or −45° (near the nozzle) by rotating the detector around the isocenter. To measure the variation of the PG spectra as a function of azimuthal angle, we rotated the detector around the beam axis by 0°, 45°, 90°, 135°, and 180°. We then simulated single monoenergetic pencil beams with energies of 50, 100, 150, and 200 MeV. The MC calculations were performed to score the PG interactions in the HPGe detector, and the corresponding energy spectrum histograms with the energy range of 0 to 7 MeV were binned with 10-keV width as a function of the energy deposited by each gamma interacting in the detector for each location and for each proton beam energy, in both the water phantom and the patient.

The PG detection rate for the water phantom was studied as a function of the angular location of the detector. For each detection rate calculation of total gamma rays, the spectrum was normalized to the total number of incident protons delivered per 2 Gy fraction of ~10⁸ [34] in the simulation, and the energy spectrum was then integrated to determine the total number of PG rays detected per incident proton. Note that the number of gamma rays from the 0.511-MeV gamma line was not counted. Similarly, for the PG detection rate of the elemental line from ¹⁶O, the area under the 6.13-MeV peak in the spectrum was calculated as the total ¹⁶O gamma rays per incident proton. Finally, we calculated the fraction of gamma rays originating from ¹⁶O. For PG detection rate calculations, the ~6% of extra attenuation corrections along a 45° gamma ray that goes through the water phantom edge was applied to the detector response [35]. Note that the 6% is simply applied for the corresponding detection rate as a simple correction representing a maximum for a point detector, but the real attenuation would be a convolution over the phantom path length distribution for all detected photons.

For the patient CT data set study, the delivery of a pristine Bragg peak used for patient treatment was simulated for a beam with 26.2 cm of range (energy at nozzle entrance: 220
MeV) by using the thinnest segment of the modulator wheel track corresponding to the IBA double-scattering option B8 [36].

Results

Angular Dependence of Detector Position on the PG Spectrum from the Water Phantom

Figure 4 shows the calculated PG energy spectrum recorded by the HPGe detector located at various polar angles (Figure 1B) with respect to the water phantom irradiated with proton beam energies of 50, 100, 150, and 200 MeV. Each spectrum was normalized to the incident proton number. For the lowest proton energy studied, 50 MeV, no significant variations were found in both the total PG and $^{16}$O gamma spectra for the 3 polar angles that were simulated. However, for higher proton beam energies (larger beam ranges), as the polar angle decreased the detection rate for both the total gamma rays and $^{16}$O emission significantly increased because the detector located in the proximal region has larger subtended solid angle covering photons produced along the beam path, and back-scatter photon cross-section could be larger at higher energy proton beam. Further quantification of the detection rate responses to various angular positions of the detector will be discussed in the subsection entitled, “Detection Rates of Total PG and $^{16}$O Gamma Rays.”

As shown in Figure 5, no variation occurred in the PG spectra over azimuthal angles of 0°, 45°, 90°, 135°, and 180°. Note that only the PG spectra for the 150-MeV proton beam are shown. Similar results were observed for the other proton energies of 50, 100, and 200 MeV (results not shown).

Patient CT Data Set Studies

Figure 6 shows the PG emission energy spectra recorded in the HPGe detector positioned at various polar angles for the patient, using a double-scattered proton beam of 220 MeV. The energy spectrum was normalized to the number of incident protons. As in the water phantom study, the PG detection rate slightly increased as the detector was moved closer to the nozzle. Further quantification of the detection rate to various angular positions of the detector will be shown in the subsection entitled, “Detection Rates of Total PG and $^{16}$O Gamma Rays.” For azimuthal angle, no variations were observed as in the water phantom.
Impact of Proton Beam Energy on PG Emission from the Water Phantom

Figure 7 shows the PG emission energy spectrum scored (1) in the HPGe detector positioned at a 0° polar angle and (2) inside the water phantom. As proton beam energy increases, the detection rate for both the total gamma rays and $^{16}$O emission increases because PG rays are produced over a larger range in the phantom (~25 cm for the 200-MeV proton beam and ~2.5 cm for the 50-MeV proton beam). In particular, the relative production of PG gamma rays from the $^{16}$O elemental line as a function of proton energy rises sharply at 50-MeV proton beam energy, which is consistent with other elemental spectral lines shown in the study by Polf et al [17]. This is mainly because for the beam energies considered in this study, the $^{16}$O gamma ray production cross-section is at its highest for the 50-MeV proton beam [30] and decreases for the higher proton beam energies used in this study, as shown in Figure 8.

Another reason for relatively high production of $^{16}$O gamma rays is the increase in low-energy PG rays produced as the proton beam passes through the longer pathway of the water phantom with higher proton beam energy. The proton beam energy also affects PG...
production from other elements. For example, the production of the $^{12}$C elemental spectrum line almost disappears for lower proton beam energy.

**Detection Rates of Total PG and $^{16}$O Gamma Rays**

To quantify the PG detection rate response to angular variation of its position, we plotted the detection rates as shown in Figure 9 for (1) total PG rays, (2) $^{16}$O gamma rays produced per incident proton, and (3) the fraction of $^{16}$O gamma production relative to total PG rays from the water phantom and from the patient during the proton irradiation, as a function of the detector location (polar angle) for various proton beam energy ranges. The detection rate per incident proton significantly increased for both the total PG rays ($2.3 \times 10^{-2}$ at $\theta = 45^\circ$ to $4.9 \times 10^{-2}$ at $\theta = -45^\circ$) and $^{16}$O gamma rays ($3.5 \times 10^{-4}$ at $\theta = 45^\circ$ to $5.6 \times 10^{-4}$ at $\theta = -45^\circ$) with the 200-MeV proton beam in the water phantom as the detector was moved closer (with decrease in the polar angle) to the nozzle. Also, detection rates per incident proton for both total PG rays and $^{16}$O gamma rays increased as the proton beam energy increased. However, the detection rate of $^{16}$O PG production relative to total PG emissions as a function of proton beam energy showed the reciprocal relationship: the fraction of $^{16}$O gamma out of total PG rays detected increased as the proton beam energy decreased. The relationship was due to the changes to the $^{16}$O...
gamma production cross-section and proton beam range in the water phantom as a function of proton beam energy, described in previous sections.

Discussion

In this work, we have characterized PG emission spectra and investigated the detector efficiency of PG emission from a water phantom and a representative patient CT data set as a function of detector angular position and as a function of the proton beam energy. As emphasized in the “Introduction,” measuring the dependence of the relative PG detection rates from the entire proton beam path in the target at various angular positions not only can be used for in vivo proton range verification, but also can provide the information on anatomic changes during the course of treatment by analyzing the characteristics of PG emission spectra.

Our results showed overall significant dependence of the detection rate on the polar angle of the detector, over the range of proton beam energies studied, both in irradiating the water phantom and the patient CT data set. As the polar angle decreased, the detection rate for both the total PG emission and the $^{16}$O gamma emission significantly increased by up to a factor of ~2 with 200-MeV proton beam energy. This is because the detector closer to the nozzle (the proximal region) collects more photons produced along the beam path in the phantom. In addition, the high-energy neutrons produced in the treatment nozzle and patient are predominantly emitted in the downstream direction (forward) from the nozzle [37], and therefore, detector placement in the backward region should further be considered to avoid detector damage due to those high-energy neutron backgrounds. For azimuthal angle, the detection rate was almost identical over all of the positions considered, indicating no azimuthal angular dependence of the PG detection rate. Because this implies that the PG detection rate from water phantom is linearly dependent on the number of detectors around the beam central axis, when using N number of detector heads around the beam line, a detection rate increase of a factor of N would be

Figure 9. Detection efficiencies for (A) total prompt gamma emission, (B) $^{16}$O gamma emission per incident proton, and (C) $^{16}$O gamma fraction to total gamma rays from the water phantom and from the patient as a function of polar angle of the detector location, with various energy ranges of proton beam. Abbreviations: CT, computed tomography; deg, degree.
expected. For patient CT data, however, internal anatomy variations in the azimuthal angles may impact on the detection rate and characteristics of PG emission spectra owing to different attenuations through different types of tissues in the body, which requires further investigation.

We observed that the detection rate per incident proton of both the total PG rays and the $^{16}\text{O}$ gamma rays increased with increasing energy of the proton beam because higher proton energy has a longer range in the target. However, the relative detection rate of $^{16}\text{O}$ gamma emission to the total PG rays detected increased as the proton beam energy decreased because $^{16}\text{O}$ elemental gamma production sharply increases at the lowest proton energy (50 MeV) used in this study.

Conclusion

As mentioned in the “Introduction” on the delivery of the double-scattered proton beam to the patient, $^{16}\text{O}$ gamma emission was shown to better match the proton dose deposition than total PG emission owing to PG emission from elements other than oxygen in the inhomogeneous anatomic structures. Therefore, using $^{16}\text{O}$ gamma emission may be more promising for in vivo proton therapy range verification. However, the relatively low detection rate of $^{16}\text{O}$ gamma production (~2 orders of magnitude) compared with total PG production must be compensated by further improvements to detector design, such as the inclusion of multiple detector heads, or significantly improved detection rates.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts of interest to disclose.

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