Feasibility study of using fall-off gradients of early and late PET scans for proton range verification

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Purpose: While positron emission tomography (PET) allows for the imaging of tissues activated by proton beams in terms of monitoring the therapy administered, most endogenous tissue elements are activated by relatively high-energy protons. Therefore, a relatively large distance off-set exists between the dose fall-off and activity fall-off. However, $^{16}\text{O}(p,2p,2n)^{13}\text{N}$ has a relatively low energy threshold which peaks around 12 MeV and also a residual proton range that is approximately 1 to 2 mm. In this phantom study, we tested the feasibility of utilizing the ^{13}N production peak as well as the differences in activity fall-off between early and late PET scans for proton range verification. One of the main purposes for this research was developing a proton range verification methodology that would not require Monte Carlo simulations.

Methods and materials: Both monoenergetic and spread-out Bragg peak beams were delivered to two phantoms — a water-like gel and a tissue-like gel where the proton ranges came to be approximately 9.9 and 9.1 cm, respectively. After 1 min of postirradiation delay, the phantoms were scanned for a period of 30 min using an in-room PET. Two separate (Early and Late) PET images were reconstructed using two different postirradiation delays and acquisition times; Early PET: 1 min delay and 3 min acquisition, Late PET: 21 min delay and 10 min acquisition. The depth gradients of the PET signals were then normalized and plotted as functions of depth. The normalized gradient of the early PET images was subtracted from that of the late PET images, to observe the ^{13}N activity distribution in relation to depth. Monte Carlo simulations were also conducted with the same set-up as the measurements stated previously.

Results: The subtracted gradients show peaks at 9.4 and 8.6 cm in water-gel and tissue-gel respectively for both pristine and SOBP beams. These peaks are created in connection with the sudden change of ^{13}N signals with depth and consistently occur 2 mm upstream to where ^{13}N signals were most abundantly created (9.6 and 8.8 cm in water-gel and tissue-gel, respectively). Monte Carlo simulations provided similar results as the measurements.

Conclusions: The subtracted PET signal gradient peaks and the proton ranges for water-gel and tissue-gel show distance off-sets of 4 to 5 mm. This off-set may potentially be used for proton range verification using only the PET measured data without Monte Carlo simulations. More studies are necessary to overcome various limitations, such as perfusion-driven washout, for the feasibility of this technique in living patients. © 2017 American Association of Physicists in Medicine [https://doi.org/10.1002/mp.12191]

Key words: ^{13}N , Monte Carlo simulation, positron emission tomography (PET), proton range verification, proton therapy, radioactive decay, tissue composition

1. INTRODUCTION

Proton therapy is one of the most effective methods of cancer treatment and is continuing to increase in popularity. Currently, proton therapy can be used to treat most body sites including head-neck, chest, abdomen and extremities. Compared to other conventional methods of radiation therapy that uses X-rays, proton therapy provides no exit dose, which accounts for the dosage found in normal healthy tissue to be substantially lower than that resulting from the other conventional therapies.

However, when uncertainties in the calculation of the proton range or errors in the actual treatment occur, a significant overdose to healthy tissues and/or underdose to a tumor can arise.¹ Therefore, clinicians usually accommodate these uncertainties as safety margins that are incorporated into their treatment plans. However, it does reduce the effectiveness of proton therapy. If uncertainties concerning the proton range were reduced, less safety margins would be required and this would lead to more effective treatment plans. In order to evaluate and eventually reduce these uncertainties and errors, various proton range verification methods have been investigated.² Among these, *in vivo* imaging of proton activated tissue using positron emission tomography (PET) is one of the most widely investigated methods.^{3–12}

A variety of PET-based treatment verification methods were implemented using modalities such as off-line, in-beam, on-line, in-room, *in situ*, and time-of-flight PET^{5,7–10,13} which offer different measurement time points (or postirradiation delay), sensitivity, geometry (or solid angle), image quality and etc. However, each of these methods has its own advantages and disadvantages. However, most (if not all) of these methods are constrained by the fact that activation is induced via nuclear interactions which have dedicated energy thresholds and most endogenous tissue elements require high-energy protons for positron-emitter activation. Therefore, a relatively large distance off-set exists between the dose fall-off and activity fall-off. This distance off-set also varies depending on postirradiation delay, PET acquisition time, tissue elemental composition, biological washout, etc., which makes proton range verification using PET challenging. However, the $^{16}\text{O}(\text{p},2\text{p},2\text{n})^{13}\text{N}$ interaction cross-section has a relatively low energy threshold (~ 9 MeV) and exhibits narrow peak at around 12 MeV [Fig. 1(a)]. At these energies, the residual proton range is only around 1 mm. This is quite a distinct property that separates it from the others considering that all other interaction cross-sections have broad peaks with approximately 20 MeV or higher interaction energy thresholds in which the residual proton ranges 5–10's of mm (Fig. 1 and Table I). In this research, we demonstrated the feasibility of using narrow $^{16}\text{O}(\text{p},2\text{p},2\text{n})^{13}\text{N}$ interaction cross-section peaks as an anchor point for proton range verification. Conventional proton range verification methods utilize Monte Carlo simulations where measured PET profiles are often compared with Monte Carlo simulated PET and dose profiles.^{1,2,4,5,10,12} A new proton range verification methodology

FIG. 1. Cross-sections of the four most abundant proton–nuclear interactions (leading to positron emissions) in the body during proton therapy (adapted from Nishio et al. 2008¹⁶). The maximum (for $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$) and mid-maximum (for all others) cross-section points used for Table I are shown as purple dashed bars. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE I. The proton energy and residual proton range in water are tabulated either for the maximum and mid-maximum point of each cross-section as shown in Fig. 1.

Cross-section	Maximum cross-section point		Mid-maximum cross-section point		Half-life
	Energy	Residual range	Energy	Residual range	
$^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$	12.0 MeV	1.7 mm	10.0 MeV	1.2 mm	9.96 min
$^{12}\text{C}(\text{p},\text{pn})^{11}\text{C}$	45.0 MeV	18.4 mm	23.0 MeV	5.5 mm	20.23 min
$^{16}\text{O}(\text{p},\text{pn})^{15}\text{O}$	35.0 MeV	11.7 mm	26.5 MeV	7.1 mm	2.04 min
$^{16}\text{O}(\text{p},\alpha\text{pn})^{11}\text{C}$	64.0 MeV	34.7 mm	43.5 MeV	17.3 mm	20.23 min

presented in this research potentially does not require Monte Carlo simulations.

2. MATERIALS AND METHODS

2.A. Phantom activation and PET imaging

A phantom consisting of three 12-cm long sections composed of high-density polyethylene (HDPE), water-gel, and tissue-gel was made (Fig. 2 and Table II). The phantom was activated using two passively scattered 116-MeV proton beams — a monoenergetic (Bragg peak dose) beam (1.6 and 4.6 Gy at entrance and peak, respectively, irradiated for 372 s) and a 6-cm spread-out Bragg peak (SOBP) beam (2 Gy at SOBP irradiated for 40 s) with a 2-hour time interval between the two irradiations. A proton field size of $7 \times 7 \text{ cm}^2$ was used to irradiate the phantom, as shown in Fig. 2. Immediately after each irradiation, the phantom was moved to a mobile PET scanner (NeuroPET, Photo Diagnostic Systems, Boxboro, MA) and imaged for 30 min in list mode with a 1-min postirradiation delay. Along the uniform proton activation region, adjacent PET voxels (each voxel size $2 \times 2 \times 2 \text{ mm}^3$) were merged to bigger and laterally

FIG. 2. A 12-cm long phantom irradiated with a monoenergetic and a 6 cm SOBP beam consists of three phantom sections. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE II. Elemental compositions (% by weight) and density of the three phantoms.

Phantom	^{16}O	^{12}C	^1H	^{14}N	Density (g/cm^3)
HDPE	0.0	85.7	14.3	0.0	0.95
Water-gel	87.61	1.04	11.03	0.32	1.01
Tissue-gel	73.98	14.94	9.62	1.46	1.13 ^a

^a1.13 and 1.104 g/cm^3 were studied for tissue-gel Monte Carlo simulations but the latter density (1.104 g/cm^3) was eventually chosen because it was in better agreement with the measurement.

integrated voxels of $2.6 \times 2.6 \times 0.2$ ($X \times Y \times Z$) cm^3 for water- and tissue-gels and $2.6 \times 5.2 \times 0.2$ ($X \times Y \times Z$) cm^3 for HDPE where Z is the length-wise direction along each section of the phantom. PET signals in each integrated voxel were then averaged and depth activity (or PET signals) curves were obtained. Standard deviation of each integrated voxel was calculated for future analysis. PET data were acquired in list mode and images were reconstructed with a 3D ordered subset expectation maximization (OSEM) algorithm (five iterations, four subsets, and 0.3 mm Gaussian filter) using different time frames. The details of the PET data acquisition and reconstruction methods can be found in other publications that used a mobile PET scanner.^{6,10,14} The mobile PET scanner's specification and performance measurement based on NEMA standard is also available in a different publication.¹⁵ The system sensitivity is 18.8 cps/kBq in the center and 21.6 cps/kBq at 10 cm off the center of FOV.¹⁵

2.B. Monte Carlo simulation

The monoenergetic and SOBP proton beams that had been used in the phantom activation study were simulated using Geant4.¹⁶ The Monte Carlo simulated proton energy fluence at each phantom voxel was then convolved¹⁷ with the proton-nuclear interaction cross-section data from Nishio et al. 2008¹⁸ in order to create radionuclides in each voxel. The activity of each radionuclide (^{11}C , ^{13}N , and ^{15}O) was retrieved based on the irradiation time for activity build-up (with simultaneous decay) and postirradiation delay (for decay) and PET acquisition time (for activity summation) and the three radionuclides' activities were summed to construct depth activity (PET) profiles.

For simplicity, only the four most abundant proton interactions leading to positron emissions were simulated (Fig. 1) which are responsible for approximately 97% of the total activity. Although the cross-sections of proton-nitrogen interactions such as $^{14}\text{N}(\text{p,pn})^{13}\text{N}$ and $^{14}\text{N}(\text{p},\alpha)^{11}\text{C}$ cannot be ignored, the abundance of nitrogen in human tissues averages to be around 2 to 3% which makes proton-nitrogen interaction insignificant in the consideration of the total activity. All four cross-sections used for Monte Carlo (MC) simulations were derived from a semi-empirical equation,¹⁹ which is in agreement with the experimental data²⁰ available at the EXFOR library.²¹ Depth dose as well as depth activity were Monte Carlo simulated using identical set-ups as measurements. Three phantom materials were simulated according to their elemental compositions and measured physical densities. However, the tissue-gel material was Monte Carlo simulated with two different physical densities (1.130 and 1.104 g/cm^3) in order to find Monte Carlo simulated depth activity profiles that are in better agreement with the measurements.

A 7-mm FWHM 3-D Gaussian convolution kernel is generally used in other research^{6,10} to account for the spatial resolution (7 mm FWHM) of the mobile PET scanner and this would also account for potentially applied smoothing during image reconstruction. However, no Gaussian convolution kernel was used purposely in this research in order to simulate depth-dependent radioisotope production without the blurring caused by limited PET spatial resolution. Monte Carlo simulation was performed throughout the study to the level that standard deviation (error bars) are $\ll 1\%$ of the data values.

2.C. Analysis of depth activity information

The 3 min PET acquisition after 1-min postirradiation delay was named "First 3 min PET" and 10 min PET acquisition after 21-min postirradiation delay was named "Last 10 min PET" for each phantom section. A gradient was calculated with depth for each PET (or depth activity) profile. The purpose of the gradient calculation was to compare the subtle differences in the activity fall-off slope (or gradient) between early PET scans (such as first 3 min PET) and late PET scans (such as last 10 min PET). Two gradients from early and late PET scans were normalized to the maximum value and the early scans were then subtracted from the late scans to find the specific depth where distinctly different gradients (or slopes) are located. Pooled standard deviations from the first 3 min and last 10 min PET were propagated to generate error bars for the subtracted gradients.

The entirety of the above procedures was repeated with different early and late PET scan time schemes — "First 10 min PET" and "Last 20 min PET" as well as "First 15 min PET" and "Last 15 min PET" in order to test the sensitivity of the proposed method for different PET acquisition time and postirradiation delays. Statistical analysis was performed throughout the study. However, error bars were generated in selected figures only for easier viewing of the figures with that had multiple graphs in close proximity to one another.

3. RESULTS

3.A. Activity fall-off comparison between early and late PET scans

Figure 3 shows the normalized depth activity profiles from early (first 3 min) and late (last 10 min) PET scans of three phantom materials irradiated by a monoenergetic proton beam. The maximum activity concentrations were 1501 counts/cm³ for the first 3 min and 2178 counts/cm³ for the last 10 min for HDPE, both of which were normalized to 1. Similarly, there were 5976 and 1384 counts/cm³ for the water-gel and 5913 and 2019 counts/cm³ for the tissue-gel. HDPE shows virtually no difference between the two PET scans in both the location and gradient of activity fall-off [Fig. 3(a)] considering ¹¹C is the only dominant radioisotope created in the proton-HDPE (or ¹²C) interaction and no depth-dependent changes of positron emission are expected over time (after ignoring very minor contributions from ¹⁰C from ¹²C(p,pn)¹⁰C interaction). The water-gel shows considerable differences between the two PET scans in which the last 10 min PET shows a less steep gradient and a smaller 50% activity fall-off depth [Fig. 3(b)]. While the first 3 min PET profile is mostly from quickly decaying ¹⁵O radioisotopes created from ¹⁶O(p,pn)¹⁵O which is rather steep in gradient around the mid-maximum cross-section region (purple dashed bar in Fig. 1) with moderate residual proton ranges (Table I), the last 10 min PET profile is mostly from slowly decaying ¹¹C radioisotopes where ¹⁶O(p,αpn)¹¹C is less steep and also located at the higher energy region (Fig. 1) with

relatively large residual proton ranges (Table I). The combination of these effects reduced the gradient of the last 10 min PET activity fall-off and also shifted it proximally. The tissue-gel shows less differences due to the substantial presence of ¹²C in the tissue-gel [Fig. 3(c)]. While the first 3 min PET profile is also mostly from quickly decaying ¹⁵O radioisotopes created from ¹⁶O(p,pn)¹⁵O, the last 10 min PET profiles are mostly from the summation of ¹¹C radioisotopes created from both ¹⁶O(p,αpn)¹¹C and ¹²C(p,pn)¹¹C interaction cross-sections. ¹²C(p,pn)¹¹C's steep gradient and relatively short residual proton range (at the mid-maximum cross-section point) reduces the effect of ¹⁶O(p,αpn)¹¹C, which has a less steep gradient and relatively large residual proton ranges (Fig. 1 and Table I).

3.B. Comparison of measurements and Monte Carlo simulations

Figure 4 shows the comparison of measurements and Monte Carlo simulations of the first 3 min and last 10 min activity depth profiles. For the HDPE phantom measurements irradiated by monoenergetic and SOBPs proton beams, no noticeable difference was observed between the first 3 min and last 10 min PET scans [Figs. 4(a) and 4(b)]. Monte Carlo simulations provided identical activity profiles considering that ¹¹C is the only radioisotope generated in this simulation and therefore, no time dependence is observed. For the water-gel Monte Carlo simulation, while the first 3 min PET (Monte Carlo simulation) is in concordance with the

FIG. 3. Depth activity profiles for first 3 min and last 10 min PET, normalized to the maximum value. (a) HDPE shows no difference in gradients or distance offset between two PET scans at the fall-off region, (b) Water-gel shows moderately different gradients and an offset of ~4 mm at 50% distal activity, (c) Tissue-gel shows slightly different gradients and an offset of ~1.5 mm. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 4. Measurement and Monte Carlo simulation comparisons for the first 3 min and last 10 min activity depth profiles. Depth dose profiles were overlaid for comparison with all profiles normalized to their maximum value. (a)/(b) HDPE phantom irradiated by a monoenergetic/SOBP proton beam. (c)/(d) Water-gel. (e)/(f) Tissue-gel. [Color figure can be viewed at wileyonlinelibrary.com]

measurement, the last 10 min PET (Monte Carlo simulation) does not agree [Fig. 4(c)]. Instead, it shows a concave local maximum (at 9.6 cm) in the middle of the distal fall-off

region. This local maximum coincides with the depth where the largest amount of ^{13}N is created according to $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$ interaction. Its concave shape with a peak is from the

uniquely shaped $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$ interaction cross-section (Fig. 1). It is also interesting to note that this depth is 1 mm proximal to the Bragg peak depth (at 9.7 cm), which agrees with the residual ranges of protons from the mid-maximum and maximum $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$ cross-section region (Table I). Figure 4(d) shows a similar trend for the water-gel irradiated by an SOBP beam but in a less pronounced manner. Monte Carlo simulations of the tissue-gel [Figs. 4(e) and 4(f)] do not demonstrate noticeable differences within the measurements as shown in the water-gel. It is due to the presence of ^{12}C in the tissue-gel phantom which creates ^{11}C when irradiated by protons. ^{11}C radioisotopes contribute as being the majority of the last 10 min PET signals and $^{12}\text{C}(\text{p},\text{pn})^{11}\text{C}$ cross-section has a relatively low energy threshold. Therefore, the ^{11}C radionuclides created smears the ^{13}N 's distinct concave-shaped production profile at the fall-off region.

3.C. Comparison of subtracted activity gradients with proton range

Figure 5 shows normalized depth gradients concerning the depth activity profiles of the first 3 min PET and last 10 min PET of three different phantom materials. The subtractions of two gradients “Gradient (Last 10 min PET) – Gradient (First 3 min PET)” show the depths in which the largest gradient differences are located. Both the first 3 min

and last 10 min PET measurements show sharp gradient falls at the distal activity fall-off region in HDPE [Figs. 5(a) and 5(b)]. However, when subtracted, no distinct differences are observed [Figs. 5(c) and 5(d)]. For the water-gel measurements, the last 10 min PET show activity fall-offs that are considerably less steep [Figs. 5(e) and 5(f)], as observed and discussed previously in Figs. 3(b) and 4(c). Therefore, the subtracted gradients show distinct peaks at a depth of 9.4 cm [Figs. 5(e) and 5(f)]. When compared with the depth dose profiles, this peak is located 5 mm and 4 mm proximal to the range (defined at 90% distal dose) for a monoenergetic and SOBP beam, respectively. Monte Carlo simulations show identical results as the measurements found [Figs. 5(g) and 5(h)]. It is also interesting to note that the subtracted gradient peaks are located 2 mm proximal to the location where ^{13}N was most abundantly created. The peak's proximal off-set is partly due to the fact that the maximum gradient of the ^{13}N production profile occurs proximally to its maximum production depth. This location (where ^{13}N was most abundantly created) is shown as concave peaks at 9.6 cm in Monte Carlo simulated last 10 min PET profiles [Figs. 4(c) and 5(g)]. For the tissue-gel measurement, the last 10 min PET scans show slightly less steep gradients at the activity fall-off region [Figs. 5(i) and 5(j)]. The subtracted gradients show a less

FIG. 5. Depth activity and gradient profiles of first 3 min and last 10 min PET scans, normalized to the maximum value. (a)–(d) HDPE phantom. (e)–(h) Water-gel. (i)–(l) Tissue-gel. For water-gel and tissue-gel, the subtracted gradient peaks are located 4 to 5 mm proximal to the proton range. [Color figure can be viewed at wileyonlinelibrary.com]

pronounced peak at a depth of 8.6 cm, located 5 mm and 4 mm proximal to the 90% distal dose range of monoenergetic and SOBP beams, respectively. The Monte Carlo simulations also show identical results [Figs. 5(k) and 5(l)].

In summary, the proton ranges are located 4 to 5 mm distal to the gradient peak depths for both water-gel and tissue-gel. Table III shows the complete list of depths and distance off-sets mentioned above. The tissue-gel Monte Carlo simulation results presented here are for the tissue-gel phantom simulated with the physical density of 1.104 g cm^{-3} and agreed well with the measurements (gradient peaks were found at identical depths).

The entirety of the above measurements and Monte Carlo simulations were repeated with “First 10 min PET” and “Last 20 min PET” scans as well as “First 15 min PET” and “Last 15 min PET” scans and they provided similar shaped peaks located at the identical depths as found in this research, however, in somewhat smaller magnitudes.

For completeness, the above processes were repeated for selected cases of Monte Carlo simulations performed with a 7-mm Gaussian convolution kernel and Poisson noise (Appendix Fig. A1) and were compared with the measurement. They showed slightly worse but very similar agreement compared with Monte Carlo simulations performed without Gaussian kernel or noise.

3.D. Analysis of three progeny radioisotopes (^{15}O , ^{13}N , and ^{11}C) using Monte Carlo simulation

Figure 6 shows normalized Monte Carlo simulated depth activity profiles of early (first 3 min) and late (last 10 min) PET scans and the relative activities of three different radioisotopes (^{15}O , ^{13}N , and ^{11}C) in water and tissue-gels. As discussed previously, the maximum ^{13}N creation is observed at a depth of 9.6 cm for the water-gel. Although it was not observed previously, the maximum ^{13}N creation is observed at a depth of 8.8 cm for the tissue-gel.

Figure 7 contrasts the time activity curves and the relative activities of three different radioisotopes (^{15}O , ^{13}N , and ^{11}C) at two depths near minimum and maximum ^{13}N

creation was observed. Time activity curves show percent contribution of each isotope relative to the total starting activity (at the shallower depth). The relative activities show the contribution of each isotope to the activity at each time point. Please note that all early PET scans started with 1 min postirradiation delay. For the case of water-gel irradiated by the monoenergetic proton beam which showed the most prominent peak [Figs. 5(e) and 5(g)], there is a clearly higher contribution of ^{13}N at a depth of 9.6 cm [Figs. 7(b) and 7(d)] compared the data found at a depth of 8.6 cm [Figs. 7(a) and 7(c)]. All three different early PET (first 3 min, first 10 min, and first 15 min PET) and late PET (last 10 min, last 20 min, and last 15 min PET) scan durations were intended to acquire single, predominant radioisotopes with minimum amount of overlap with other isotopes. This attempt was most successful at a depth of 9.6 cm where early PET scans predominantly contain ^{15}O while the late PET scans contain mostly ^{13}N [Fig. 7(d)]. For simplicity in illustration, only a single combination of early and late PET scans was overlaid with each figure. However, all nine combinations were applied to all irradiation conditions (water- or tissue-gel irradiated by monoenergetic or SOBP proton beam).

First 3 min/last 10 min combination was found to be most suitable for the proposed method although the first 15 min/last 15 min provided very similar results. Please note that the proposed method utilizes the difference in activity fall-off gradients between early and late PET scans for proton range verification. The maximized difference in activity fall-off gradients leads to more accurate proton range verification. To maximize the difference, it is important to acquire each (early and late) PET scan with dominant radionuclide(s) in each scan with minimum contribution from other radionuclides. In particular, the first 3 min/last 10 min combination was successful in separating ^{15}O and ^{13}N radionuclides as dominant radionuclides in early and late PET scans respectively with minimum cross-contribution. Although the first 15 min/last 15 min combination provides less separation of ^{15}O and ^{13}N radionuclides, higher signal to noise ratio (due to longer scan time) appears to overcome the inferior separation.

TABLE III. Comparison of maximum subtracted gradient depths with the proton range (as Bragg-peak depth for monoenergetic proton beams and 100%/90% distal dose range for SOBP proton beams). Identical results were obtained for both “First 3 min/last 10 min PET” and “First 10 min/last 20 min PET”.

	Gradient (10 min)- Gradient (3 min) peak depth	Bragg peak (Mono)/ 100% distal dose range (SOBP beam)	90% distal dose range	Distance off-set
Water-gel/Mono/Measurement	9.4 cm	9.7 cm	9.9 cm	−3 mm/−5 mm
Water-gel/Mono/Monte Carlo	9.4 cm	9.7 cm	9.9 cm	−3 mm/−5 mm
Tissue-gel/Mono/Measurement	8.6 cm	8.9 cm	9.1 cm	−3 mm/−5 mm
Tissue-gel/Mono/Monte Carlo	8.6 cm	8.9 cm	9.1 cm	−3 mm/−5 mm
Water-gel/SOBP/Measurement	9.4 cm	9.4 cm	9.8 cm	0 mm/−4 mm
Water-gel/SOBP/Monte Carlo	9.4 cm	9.4 cm	9.8 cm	0 mm/−4 mm
Tissue-gel/SOBP/Measurement	8.6 cm	8.6 cm	9.0 cm	0 mm/−4 mm
Tissue-gel/SOBP/Monte Carlo	8.6 cm	8.6 cm	9.0 cm	0 mm/−4 mm

^aMono stands for monoenergetic proton beam.

FIG. 6. The relative depth distribution of three progeny radioisotopes (^{15}O , ^{13}N and ^{11}C) in (a)/(b) water-gel and in (c)/(d) tissue-gel calculated using Monte Carlo simulations. The ^{13}N peaks are only pronounced for gels irradiated by a monoenergetic proton beam. Two (dashed and solid) bars represent two depths in terms of the near minimum and near maximum ^{13}N creations were observed. Curves are normalized to the maximum total PET value. [Color figure can be viewed at wileyonlinelibrary.com]

For the case of the tissue-gel irradiated by the SOBP proton beam which showed the least prominent peak [Figs. 6(e) and 6(f)], there is a higher contribution of ^{13}N at a depth of 8.8 cm [Figs. 7(f) and 7(h)] compared to a depth of 7.8 cm [Figs. 7(e) and 7(g)], however, it is not as dominant as in the water-gel shown above. The reason being that first, the magnitude of ^{13}N time activity curve is two to three times smaller (starting with 12% in Fig. 7(b) versus 5% in Fig. 7(f)); second, there is a major overlap (or contamination) with the ^{11}C signals.

These limitations contribute toward the bigger uncertainties in proton range verification in the cases in which the noisy parts of the subtracted gradients have a greater magnitude than the true peak (the subtracted gradient peak located 2 mm proximal to the location where ^{13}N was most abundantly created). Also, as illustrated in Figs. 8(a) and 8(b), the

sizes of the standard deviations (error bars) are large due to the propagation of errors augmented from splitting the PET signals into smaller time frames. Although visual assessment is able to distinguish the true peak for this particular case, it would be impractical when dealing with an extremely large number of datasets such as when the full beam's eye view proton range profiles are acquired. Therefore, two possible automated methods for determining the peak are suggested below.

3.E. Strategies for more reliable proton range verification

For all datasets analyzed in this research, all true peaks coincided with early PET scans' gradient valleys (minimum points) or occurred only a few millimeters downstream of the

FIG. 7. Change of activity in respect to time for three progeny radioisotopes created in gel phantoms after proton irradiation. Time activity curves/relative activities of ^{15}O , ^{13}N , and ^{11}C in water-gel at depths of (a)/(c) 8.6 cm and (b)/(d) 9.6 cm. Time activity curves/relative activities of ^{15}O , ^{13}N , and ^{11}C in tissue-gel at depths of (a)/(c) 7.8 cm and (b)/(d) 8.8 cm. [Color figure can be viewed at wileyonlinelibrary.com]

FIG. 8. (a)–(d) Comparison of subtracted gradients with depth-squared weighted subtracted gradients. Error bars are illustrated as $\pm$ standard deviation. [Color figure can be viewed at wileyonlinelibrary.com]

valleys. Therefore, peaks can be registered as being “true” only when they coincide with early PET’s gradient valleys or is located downstream within a few millimeters. Alternatively, the entire subtracted gradient profiles can be multiplied with depth or depth-squared in order to weigh the true peaks located at the greatest depths while suppressing the noisy parts located at the shallower depths. Figure 8(a) through 8(d) contrasts the subtracted gradients and depth-squared weighted subtracted gradients. While both these show peaks at the same depths, depth-squared weighted subtracted gradients suppressed the noisy parts located at the shallower depths.

The depth-squared weighting, however, increases the noise and error bars at depths deeper than the true peaks. A major reason for these large error bars is due to very small PET signals found at these depths. Therefore, these error bars can be suppressed using the fact that all true peaks occur over the distal activity fall-off region. By suppressing all data points outside the activity fall-off region (such as 90–20% or 70–10%) to zero, the true peaks can be distinguished with less influence stemming from noise. This suppression, however, can introduce some bias considering that shifts of the Bragg peak outside this region cannot be detected anymore.

4. DISCUSSION

In this study, we tested the feasibility of using ^{13}N signals as anchor points in estimating proton ranges. The $^{16}\text{O}(p, \alpha)^{13}\text{N}$ cross-section is distinctly narrow and peak shaped, and it is located in the low proton energy range. Distinctly peaked ^{13}N signals are not normally observed separately partly owing to the contribution of other radioisotopes and the smearing of signals due to the limited spatial resolution of PET scanners. Three-dimensional Gaussian convolution kernels function as smearing, therefore, Monte Carlo simulation with the addition of a 3-D Gaussian convolution kernel, to simulate the spatial resolution loss in PET imaging, show similar activity distributions to the measurements (in other words, no distinctly peaked ^{13}N signals are observed). However, by intentionally performing Monte Carlo simulations without using 3-D Gaussian convolution kernels, we were able to observe ^{13}N ’s distinct production peaks located at the distal fall-off region in the water-gel. By comparing two PET scan schemes — early and late PET scans, we were able to contrast the change of activity in the fall-off gradients. The early PET scan signals are predominantly from quickly decaying and steep ^{15}O signals while the late PET scan signals are predominantly from slowly decaying and less steep ^{11}C signals with

additional contribution from ^{13}N . Therefore, when the gradients of the depth activity profiles were plotted, discernable differences were observed in the activity fall-off region between early and late PET scans. This difference peaked (or maximized) toward the end of the activity fall-off which correlated with both the Bragg peak and proton range showing a distance off-set of 4 to 5 mm. Therefore, it may be possible to utilize this maximum gradient difference at the fall-off region as an anchor point in estimating the proton range, without the need for Monte Carlo simulations. The proposed method is expected to work for proton beams of different initial energies considering that the proton energy degrades in similar manners at the fall-off region.

The potential gain of the proposed method is beyond simply detecting very small signals that are a few mm closer to the Bragg-peak depth than, for example, the 50% activity fall-off depth. The 50% activity fall-off depth is subject to change in complicated manners with the introduction of various variables such as postirradiation delay, PET acquisition time, organs, tissue heterogeneity, perfusion-driven wash-out, etc. However, the proposed method is based on the unique change of the activity fall-off gradient between early and late PET scans where the depth of the maximum gradient change can be correlated with the maximum ^{13}N creation depth, the Bragg-peak depth, and the proton range with tight distance off-sets (e.g., 2 mm). According to our research, such distance off-sets were consistent irrespective of phantom materials (water- and tissue-gel), proton beams (monoenergetic and SOBP), postirradiation delay (results are not shown here) and PET acquisition times. These tight distance off-sets are still subject to change with some of the above mentioned variables — organs, tissue heterogeneity, and perfusion-driven wash-out. However, this uncertainty is expected to be smaller than when correlating, for example, 50% activity fall-off depths and the proton ranges (due to the relatively large distance off-sets).

It is plausible to argue that the activity fall-off gradient itself can be used for proton range verification. Particularly for HDPE (which cannot use the gradient difference since its early and late PET scans are identical), the steepest gradient location (or the minimum valley point) and proton range can be correlated with some distance off-sets [Figs. 4(a), 4(b), 5(a), and 5(b)]. However, this approach does not seem universally applicable since the minimum (steepest) gradient locations from some early (3 min) PET scans do not have clearly defined minimum (they are rather observed as flat minimum areas) in measurements [Figs. 5(e), 5(f) and 5(j)] although they are clearly observed in Monte Carlo simulations [Figs. 5(g), 5(h), 5(k), and 5(l)]. This approach, however, is somewhat similar to a more clinically established approach which compares Monte Carlo simulated activity and measured activity for proton range verification.²²

There are several limitations that can be found in this research. Although Monte Carlo simulated depth dose profiles in water were verified with the measurement data, depth dose profiles used in HDPE, water-gel and tissue-gel were Monte Carlo simulated without measurement verification (depth dose measurements were not possible in gel

phantoms). Due to the negligible difference between water and water-gel in composition and density, gradient difference peaks were observed at the same depth for both measurement and Monte Carlo simulations. However, for the case of tissue-gel, a 2-mm difference was observed between the measured peak and Monte Carlo simulated peak when the tissue-gel was simulated with the measured physical density (1.13 g cm^{-3}) of the phantom. However, when this density was reduced by 2.3% (1.104 g cm^{-3}) for the Monte Carlo simulation, the measured and Monte Carlo simulation peaks agreed (0 mm difference). Using the reduced density for Monte Carlo simulations also provided better agreement with measured depth activity profiles. For example, Monte Carlo simulated activity fall-offs (at the 30 to 60% region) agreed with measurements within 1 mm when simulated with 1.104 g cm^{-3} while this increased to 3 mm when simulated with 1.13 g cm^{-3} . One possible explanation is unintentional heterogeneity (such as air pockets) introduced in the tissue-gel that could occur during the gelling process. This may have increased proton ranges in the tissue-gel which could be amended by simulating a tissue-gel with a lower density.

Monte Carlo simulations performed with a 7-mm Gaussian convolution kernel (with or without Poisson noise) improved but still provided a more steep gradient change in the fall-off region when compared with the measurement (Appendix Fig. A1(a)). To eliminate the possibility of the ^{16}O (p, α) ^{13}N cross-section used in this research being unrealistically sharper than the true cross-section, we compared the cross-section used in this research with seven experimentally measured cross-sections (Appendix Fig. A2). However, they show similar sharpness. An alternative explanation could be the smearing of PET signals over time due to diffusion of water in gels.²³

Another limitation of this study is the relatively large error bars as illustrated in Figs. 8(a) through 8(d). Fragmenting the original PET signals into multiple reconstruction (dealing with smaller time intervals) durations increased the Poisson noise and therefore the size of the error bars is large enough to encompass the noisy parts of the subtracted gradients. As demonstrated in Appendix Fig. A1(d), the added Poisson noise slightly increased the off-set distances (5 mm) while all other SOBP results show 4 mm off-sets (Fig. 5 and Table III). It may be safe to estimate the shift with an added ± 1 mm uncertainty with increased noise, which is 4 ± 1 mm shifts for SOBP and 5 ± 1 mm shifts for monoenergetic beams. Additionally, PET integrated voxels used for this research is relatively large (1.35 cm^3) and the uncertainties are expected to increase for smaller integrated voxels. The possible remedy for these things could be using a more sensitive PET scanner (which uses a denser and more efficient crystal, for example) or using a smaller postirradiation delay (by using in-beam PET, for example) that will increase the net PET signals.

As scanning beams (versus passive scattered beams used in this research) are becoming more common, the applicability of the proposed method in scanning beams should be examined. The need for early and late PET scans (which required a

30 min PET scan in the proton treatment room) is another limitation of this research which may affect the clinical workflow. One way to minimally affect the clinical workflow is performing an early PET scan (~3 min) with some sort of in-beam or mobile PET scanner located inside the treatment room followed by a late PET scan (~10 min) with an offline PET scanner located outside the treatment room. However, this does not solve the washout issue in terms of the late scan. More investigation is needed to reduce the scan time of the PET.

To test the usability of this technique in terms of real patients, *in vivo* studies performed on living subjects are necessary. *In vivo* studies are expected to be challenging, partly due to washout dealing with natural biological activity which depends not only on activated organs^{24–29} but also on the type of radioisotopes.^{30,31} Especially, ^{13}N signals are expected to smear over time and eventually lose its sharpness due to perfusion-driven washout (at a faster rate in soft-tissues than in bones, for example). The current study discusses the cause of time dependence of depth activity profiles in connection with different cross-sections and their progeny radioisotopes. Although the *in vivo* applicability of the proposed method is learned to be difficult, the time dependence of depth activity profiles in these kinds of “ideal” phantom situations may possibly be used as a baseline in understanding activity profiles.

APPENDIX

FIG. A1. Three different MC simulations of activity profiles in water-gel performed with 1) none of the following, 2) a 7-mm Gaussian convolution kernel, and 3) a 7-mm Gaussian convolution kernel + Poisson noise were compared with measurements. Poisson noise was created arbitrarily using $\lambda = 1$ and 3% and 5% of maximum PET signal for the first 3 min and last 10 min PET profiles, respectively. (a) Activity profiles for a monoenergetic beam. (b) Activity profiles for a SOBP beam. (c) Activity gradient profiles for a monoenergetic beam. (d) Activity gradient profiles for a SOBP beam. [Color figure can be viewed at wileyonlinelibrary.com]

5. CONCLUSIONS

Subtracted PET signal gradient peaks and the proton ranges for water-gel and tissue-gel show consistent distance off-sets of 4 to 5 mm. These off-sets may possibly be used for proton range verification using only measured PET data and would potentially remove the need for Monte Carlo simulations. More studies are necessary to overcome various limitations such as perfusion-driven washout and eventually to test the feasibility of this technique for living patients.

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CONFLICT OF INTEREST

None.

FIG. A2. Comparison of the semi-empirical $^{16}\text{O}(p,\alpha)^{13}\text{N}$ cross-section (Nishio et al.)¹⁹ used in this research with the experimentally measured cross-sections. [Color figure can be viewed at wileyonlinelibrary.com]

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