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Feasibility of Using Distal Endpoints for In-room PET Range Verification of Proton Therapy

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Abstract

In an effort to verify the dose delivery in proton therapy, Positron Emission Tomography (PET) scans have been employed to measure the distribution of β^+ radioactivity produced from nuclear reactions of the protons with native nuclei. Because the dose and PET distributions are difficult to compare directly, the range verification is currently carried out by comparing measured and Monte Carlo (MC) simulation predicted PET distributions. In order to reduce the reliance on MC, simulated PET (simPET) and dose distal endpoints were compared to explore the feasibility of using distal endpoints for in-room PET range verification. MC simulations were generated for six head and neck patients with corrections for radiological decay, biological washout, and PET resolution. One-dimensional profiles of the dose and simPET were examined along the direction of the beam and covering the cross section of the beam. The chosen endpoints of the simPET (x-intercept of the linear fit to the distal falloff) and planned dose (20–50% of maximum dose) correspond to where most of the protons are below the threshold energy for the nuclear reactions. The difference in endpoint range between the distal surfaces of the dose and MC-PET were compared and the spread of range differences were assessed. Among the six patients, the mean difference between MC-PET and dose depth was found to be -1.6 mm to $+0.5$ mm between patients, with a standard deviation of 1.1 to 4.0 mm across the individual beams. In clinical practice, regions with deviations beyond the safety margin need to be examined more closely and can potentially lead to adjustments to the treatment plan.

Keywords

Index Terms; proton beams; PET; hadron therapy

I. Introduction

Proton therapy offers a highly conformal dose delivery due to the Bragg peak. However, because most of the dose is delivered in the steep falloff region, there is greater sensitivity to the uncertainty in the range. Planning a proton beam treatment involves using empirical evidence to convert the Hounsfield units of a CT scan into proton stopping power. Inaccurate conversions can lead to range uncertainties and an under-dose to the tumor or over-dose to a critical organ. Other uncertainties in the dose range can come from organ motion, anatomical changes, and inexact patient positioning. Better knowledge of the extent of dose range deviations from treatment plans is needed to optimize proton therapy on an individual level and to verify dose delivery. Currently used safety margins are typically a percentage of the dose range and an additional millimeter or two. E.g., those used at Massachusetts General Hospital (MGH) are 3.5% + 1 mm [1]. Range deviations outside this margin are of greatest concern.

Positron Emission Tomography (PET) scans performed soon after proton therapy are being studied as a means of verifying the delivery location of the planned dose by imaging radioisotopes created by proton-nucleus interactions [2]–[12]. PET activity can be generated through several nuclear reaction channels each with different threshold energies. The main channels are listed in Table I. The measured PET activity distribution contains contributions from mixed radionuclide species, most importantly ^{15}O and ^{11}C . ^{15}O has the highest production rate but a very short half-life (2.037 minutes), and therefore is the dominant contribution in PET scans taken during or shortly after the treatment, i.e. in-beam or short in-room PET scans [3], [9], [11]. On the other hand, ^{11}C , with a longer half-life of 20.39 minutes, is the main contributor to PET scans taken with a delay, i.e. off-line scans [2], [4]. Although the PET signal results from nuclear interactions, which is distinct from the therapeutic dose that arises mainly from electromagnetic interactions, these events occur in such tight proximity to each other that it poses an opportunity to investigate the emission of the nuclear interaction with potential clinical significance.

PET for proton range verification involves comparing two distributions, one related to the planned dose distribution before treatment, the other related to the PET measurement after treatment. Since dose and PET distributions arise from different processes, there is first the question of what can be compared, and then the question of how to do the comparison. For the former, there have been three main approaches. One of the leading methods of estimating dose range uses time-consuming (~ 6 hrs/patient [13]) Monte Carlo (MC) simulations to predict the expected activity distribution based on the planned dose which is then compared to PET measurements [2]. Note that the MC relies heavily on PET production cross sections, which are not all adequately measured [14]–[16]. Fig. 1 shows an example of the shapes of dose, PET, and MC-PET profiles in a water phantom.

Another approach, with the goal of reducing computation time, has been to convolve pre-determined 1D analytical filter functions with the planned dose profiles to generate an expected PET distribution [8], [18]. The method relies on a set of filter functions determined from functional fits to a MC-PET simulation of uniform materials, hence it also relies on the PET production cross sections. As an extension to the forward filtering, a reverse approach has been studied to recover the dose from the measured PET after deconvolving it with the 1D filter function [10], [19]. A similar, three dimensional approach using a positron-emitter

species matrix, based on proton energy fluence, has also been proposed, but the calculations involved are much more time consuming [20]. The deconvolution leads to a reconstructed dose that can be used for more than just range verification. While these methods show some promise in simulation and phantom studies, applying a deconvolution to the (typically noisy) PET data will likely result in an excessively noisy dose distribution, despite heavy regularization, making the final range determination difficult, even when comparing doses.

The question of how to do the range comparison applies to all three methods above. To calculate range deviations from the PET image, the distal positions of the last falloff in the activity distribution profiles along the beam path are typically compared [2], [7]. Some methods have focused on the feasibility using shifts in the overall PET activity distribution to detect simulated changes to the beam energy, either through trained observers [6] or with statistical methods [21]. One method of comparing individual PET and MC-PET profile ranges (or dose to filter-derived dose) involves comparing the depth of the point at which the activity has fallen to some percent of the distal maximum activity [2], [22], [23]. However, this method relies on a single point of comparison which can be unreliable, and the determination of the distal maximum, given the irregular shape of the activity in patients, is not straightforward. The application of this method to patient data found a mean of 3–6 mm with root-mean-square deviations of 4–12 mm for in-room measurements [23] and –0.1 to 2 mm for low-perfused bony structures [2] and 3.9–6.8 mm in soft tissue [4] in offline studies. Please notice that the relatively large uncertainties in in-room measurements were mainly due to the fact that the first-generation of mobile PET scanner used in the studies did not include a CT component, making it difficult to register PET and dose distributions accurately.

An improvement upon this method has been termed the shift method [12], [24], where the entire falloff of the PET and MC-PET are compared. One profile is shifted relative to the other until the difference is minimized, and the shift distance is taken as the range difference. While it no longer compares a single point, there are still difficulties in how to normalize the activity concentrations, and over what range to make the comparison. For offline-studies, mean range differences around 2–4 mm were found, with deviations over 5 mm in 33% of profiles studied, for beams stopping in soft tissue [4], and 2.2 mm for those stopping in bone. For dose to filtered-dose comparisons, a method using the smoothed gradient of the dose distribution is used to estimate the midpoint of the distal fall-off region, to accommodate the deconvolution artifacts. The average error with this method was 2–3 mm for phantoms (no patient studies have been reported yet) [10].

The objective of this study is to explore the possibility of directly and comprehensively comparing the distal falloff points of the PET activation and the planned dose without the use of MC simulations or filter functions. At a minimum, the method should be able to detect areas where the dose underor overshoots beyond the safety margins used in the treatment planning. Because there are clear energy thresholds for PET isotope production from proton interactions, the endpoint of the activity profile should coincide with the point at which the majority of protons have energy below this threshold, i.e., at the end of the dose range. These thresholds are exploited to make the direct comparison between the end of the dose deposition and the end of PET activity. The major benefit of this simplified new approach is that in vivo range could be determined without complex and lengthy Monte Carlo calculations that include additional sources of uncertainty, such as from nuclear reaction cross sections and the effect of tissue typing on proton range.

The correlation between dose and PET falloff depths has been previously studied in plastic phantoms, showing that a shift in the proton range results in a corresponding shift in the distal edge of the PET activity [25]. We have studied the feasibility of using this correlation

for point-by-point range evaluation over the cross section of the proton beam. As a proof of concept, the endpoints of the distal falloff of the planned dose were compared to the endpoints of a corresponding MC-simulated PET activity concentration to determine if a simple, consistent distance between the two can be determined in a fast, automated fashion. Range inconsistencies in PET data collected from patients can eventually be used to improve treatment accuracy and detect errors in delivery.

II. Methods

A. Range Comparison with Distal Endpoints

The range verification approach presented here compares the endpoints of dose profiles and the corresponding PET activity profiles directly. Both profiles were generated for the lines of voxels along the beam path for the full proton irradiation field. The endpoints were determined separately for the dose and PET activity profiles to correspond roughly to the depth where very few protons are above the threshold energy for the nuclear interactions creating the PET signal.

The effectiveness of this approach relies on having the majority of the activity produced from a single dominant nuclear reaction channel, and thus having only one nuclear threshold to create a clear endpoint. This is true of ^{15}O , which can only be produced through one reaction channel, while ^{11}C can be produced through three reaction channels, each with different threshold energies. Thus an ^{15}O dominance is preferred for the end-point comparison approach in order to have a clear correlation with a single proton energy threshold, i.e., a threshold energy of 16.79 MeV for the $^{16}\text{O}(\text{p,pn})^{15}\text{O}$ channel. Accordingly, in this study we evaluated this approach for short in-room PET scans of 5 minutes started 2 minutes after the treatments, when ^{15}O comprises about 80% of the activity for typical tissues (60–80% oxygen concentration), as determined from MC simulations.

The PET endpoint was set as the x-intercept of the best linear fit to the distal falloff region. The potential fitting region started at the last distal maximum and extended 2.5 cm beyond that point. The final fit range was chosen to be the range within that region that gave the best residual sum of squares, provided that it covered at least 8 voxels, in order to have sufficient degrees of freedom in the fit. A fit was chosen to avoid uncertainties in local variations that can affect ranges based on a percentage of the distal maximum. Also, the fit uses information from multiple points in the falloff curve, rather than a single point. Other functions were explored for the distal fit, but the linear extrapolation is reasonable, quick, and gives a clear indication of the end of activation. The linear fit was found to be the most consistent and independent of specific dose delivery conditions.

To avoid variations in endpoint determination caused by the shapes of simulated PET activity profiles, all the profiles were “standardized” before the linear fit was performed. First, a reverse biological washout correction was applied to the PET activity according to tissue types determined from the CT numbers and a biological washout model determined previously from carbon beam studies [3], [26]. This model has been used in most other PET studies of dose delivery. Equation 1 shows the calculation of the reverse-decay factor for a PET signal acquired in a time frame t_f , t_d seconds after an irradiation of duration T . It is based on the decay factors used in [3]:

$$F_i = \sum_j^3 \frac{k_i}{t_f(k_j)^2} f_j(e^{k_j T} - 1)(1 - e^{-k_j t_f})(e^{-k_j t_d}) \quad (1)$$

where k_i is the decay constant for isotope i , k_j is the biological+radioactive decay factor for decay speed j , and f_j is the fraction of decay at fast, medium, and slow biological speeds [26]. The simPET was divided by the factor F_i voxel-by-voxel with the biological factors determined from CT numbers. The reverse-decayed individual isotopes were then added together based on the target density of each to form the total activity without decay. While it is not ideal, it is the only complete model currently available and provides reasonable agreement with PET data from off-line measurements.

After the washout correction, the amplitude of the activity level at each voxel was scaled against the local target densities (e.g., divided by the percentage of ^{16}O per voxel), again determined from the CT numbers. Finally, the depth axis of the profile was modulated (expanded/contracted) to water-equivalent thickness by interpolation. In theory, the adjusted profiles should all have a shape similar to what would be produced in a homogeneous water volume. Fig. 2 shows the steps of standardization with an example profile. Notice that the small distal peak in the simPET disappears after the standardization. This type of small distal peak in non-standardized PET distributions is problematic for range determination methods using a distal maximum because of the ambiguity in which peak to use as the distal maximum, especially for automatic processing of multiple profiles.

The dose endpoint was chosen to be in the middle of the range between 50% and 20% of the profile maximum. For most dose profiles with steep falloffs, the 20%–50% distance is small, but for those with gentler slopes, often arising from air pockets or lateral heterogeneities, the range from 20%–50% captures those protons that “punch through” or move laterally [27], [28] and are still energetic enough to create PET isotopes. To be consistent with the PET activity profile standardization, the depth axis of the dose profile was also modulated to waterequivalent depth before the endpoint was determined.

The range difference between dose and PET was calculated by subtracting the dose endpoint from the PET endpoint. Because the 20–50% point on the dose profiles are systematically deeper than the fitted endpoint of the PET profile, a single correction factor was determined from MC studies on a homogenous gel phantom (see Sec. II-B). The intrinsic difference between dose and PET endpoints was calculated by subtracting the dose endpoint from the PET endpoint in the phantom, and the correction was applied to all range differences. After correction, a positive range difference indicates overshoot while a negative number indicates undershoot. The smaller the absolute difference, the closer the dose was to the planned delivery.

B. Modulation Dependence of the Endpoints

In proton therapy, a spread-out Bragg peak (SOBP) field is usually delivered. The modulation of the SOBP is determined by the width of the target volume, and varies between patients. The modulation can change the shapes of dose and activity profiles, and therefore can potentially affect the endpoint determination. MC simulations were used to investigate the modulation dependence of the endpoints (see Section II-C for the details of MC simulations). Modulations of 5, 20, 40, and 60 mm for a beam range of 100 mm were simulated for dose and PET distributions in a tissue phantom. The dose and PET endpoints were calculated and compared for each modulation.

The mean differences in ranges between dose and simulated PET for 400 profiles in the phantom were used to establish the intrinsic difference (and variation) between these two endpoints for the four different modulations. This difference was applied as a single correction factor for all subsequent range comparisons.

C. Patient MC Simulation Study

Monte Carlo studies were conducted to evaluate the feasibility of the direct range comparison method. A Geant4-based Monte Carlo system developed at MGH was used for all of the simulations [29]. The system was implemented with the design of the proton delivery system at MGH's Burr Proton Center [13]. A total of 4×10^7 protons from the treatment nozzle were simulated using the planning information, i.e., proton energy (range), modulation, range compensation, and aperture shape.

MC-PET simulations were generated for six head and neck cancer patients. The protons from the treatment nozzle were simulated to interact with the matter in the head based on the CT scan of the patient. The HU numbers were converted to densities and elemental compositions according to [30]. Each set of protons was used on the CT grid 40 times with different randomizations to improve the statistics. The number of activated PET isotopes was calculated by combining the proton energy in each voxel with energy dependent nuclear cross section data that was obtained [31], [32] and optimized previously [15]. The number of isotopes created was then scaled based on the expected number of protons delivered.

The five most abundant PET isotopes produced from eight reaction channels, as listed in Table I, were included in our simulations. After simulations, radiologic decay of isotopes and biologic washout were applied according to typical in-room irradiation length (30 to 90 seconds), delay time between irradiation and scanning (90 to 150 seconds), and scan duration (300 seconds). Biological washout parameters were based on those in [3], [26], same as those used for the reverse washout. The MC-PET was smoothed to a PET resolution of 7-mm FWHM with a Gaussian kernel, based on positron range and the specifications of the current in-room scanner [33], to get the final simulated PET (simPET). The grid size was reduced from 512×512 to 256×256 , closer to the size of a PET scan. The simulation at this point mimicked data from a PET scanner.

The direct range comparison was applied to the six patients after "standardizing" the simPET activity. To get full coverage of the beam volume, profiles of dose and simPET activity were compared for all lines along the beam path in which at least 30% of the overall maximum dose was deposited. (Areas with small dose deposition suffer from too little activity and high noise levels and so were not included.) The range comparisons were formed into 2D maps of the distal surface difference, showing the simPET to dose range difference in a beam's-eye-view, based on the same representation used in [23]. The maps were convolved with a sliding window of 3×3 pixels (typically 3–4mm) to acquire local means and reduce small fluctuations.

The range differences were also put into histograms, after correcting for the intrinsic difference between endpoints, to provide a quick view of the average range and the standard deviation across the surface. An average range with large deviation from zero can indicate an overall under or overshoot of the beam, possibly from incorrect beam energy. The standard deviation of the range differences indicates whether or not there are local areas of range deviation, possibly from planning imprecision, misalignment, or organ motion.

An additional modification was made to the CT image of patient D to demonstrate the range comparison when the treated volume differs from the planned volume. A block of voxels $1.8 \times 2.7 \times 1.7$ cm within the sinuses (i.e., mostly air) was replaced with a block of typical brain values, HU=40, to simulate a filled sinus. The simulation was redone with the modified CT and compared to the original treatment plan using distal surface difference maps.

D. Rabbit Study

PET data from the thigh of a euthanized rabbit, irradiated for 1.5 minutes, was taken with an in-room mobile NeuroPET scanner. The thigh was scanned two minutes after irradiation and reconstructed with a frame time of five minutes. The rabbit thigh provided PET data in a realistic, but mostly homogeneous, volume of tissue, and without the complications of biological washout. Corrections were made to “standardize” the PET activity, but without the reverse biological washout step. A range difference map and histogram were created, for three cases: between the dose and PET, between the dose and MC simulated PET, and between the PET and simPET.

III. Results

A. Modulation-Dependence of Endpoints

Fig. 3 shows dose and PET profiles for beams with a range of 100 mm but with several different SOBP modulations. The dose and PET endpoints were determined for each profile according to the methods in II-A. The figure shows that modulation has little effect on both the dose and simPET endpoints, with the standard deviation of the simPET to dose endpoint differences being less than 0.08 mm across the different modulations.

Therefore, this method should be applicable to treatment plans with a wide range of modulations without any modifications. The intrinsic difference between the dose and PET activity profiles was found to be 1.4 ± 0.1 mm (water equivalent), with the PET endpoint shallower than the dose, for all of the different modulations. A fixed correction, based on this systematic difference, was applied to the range difference map for all of the patient and animal study results.

B. Patient MC Simulation Study Results

Fig. 4 shows an example of the planned dose and simPET overlaid on a CT slice, along with a single corresponding line profile. The dose image shows the energy deposited per kilogram, based mostly on electromagnetic interactions of the protons with the tissue. The simPET shows the corresponding radioactivity produced through nuclear interactions. The distal surface difference maps and histograms for the simulated patient data are shown in Fig. 5 in a beam’s-eye-view. Reasonable agreement between the dose and simPET endpoints was found over the cross section of the proton beam for most of the patients. Among the six patients the mean difference between dose and simPET depth was found to be -1.6 to $+0.5$ mm between patients, with a standard deviation between 1.1 and 4.0 mm for individual patients. (White areas in Fig. 5 are not included in the mean/standard deviation calculation.) See Table II for the full set of results.

The effect of modifying the CT for patient D can be seen in the distal surface difference maps in Fig. 6. The figure shows the original map (left) and the map made from the simulation using the modified CT (right). The cross section where protons passed through the modified block is circled in green on both. A clear area of “undershoot” is visible in the distal surface difference map made from using the modified CT.

C. Animal Study Results

For the rabbit thigh, we found a mean PET to dose difference of 0.2 mm with a standard deviation of 2.5 mm. Fig. 7 shows the surface difference map and histogram. Similarly, when comparing the simPET to dose we found a difference of 0.07 ± 1.1 mm and when comparing the simPET to PET using distal linear fits to both we found a difference of 0.01 ± 2.5 mm. We also applied the shift method [24] to the PET and simPET and found a mean difference of 0.38 mm with a standard deviation of 3.5 mm.

IV. Discussion

The objective of this method is to provide a fast, initial, estimation of delivered dose range deviations while minimizing complications and sources of uncertainty. The idea behind doing a direct dose to PET comparison is this: While the shape of activity profiles can be affected by many factors, including elemental composition of tissues [30], nuclear reaction cross sections [15], [16], biological washout of proton induced activity [3], [4], [26], etc, in theory, the distal endpoint of an activity profile is only determined by the thresholds of nuclear reactions.

The speed of the direct dose-to-PET comparison process— all profiles from a treatment plan can be compared in less than 30 minutes on a single processor—is a significant improvement over a full MC simulation. For comparison, a statistically accurate MC simulation of 4×10^7 protons through treatment nozzle and the patient geometry, such as was used to generate the simPET activity in this study, took 12 hours on 10 dualcore CPUs, not including any range verification steps.

The rabbit study indicates that this method of comparing PET directly to dose can have similar or better results than methods comparing PET to MC-PET. However, there are a few difficulties in this simplified approach when dealing with heterogeneous volumes. Patients D–F have nasal cavity irradiations with large tissue variation, ranging from bone to brain to air, both distally and laterally. Greater heterogeneity leads to more discrepancies between the dose and PET ranges. Lateral heterogeneity complicates the endpoint estimations because protons that were assumed to have travelled entirely along a given line of voxels might actually have scattered into the path from another line of voxels and have a different average energy. With co-registration errors between the PET and the planned dose included, any true discrepancies will likely be falsely increased. In a heterogeneous region where the dose and PET are not aligned precisely, it is possible that one is comparing a line of PET that passes through more or less dense material than what is assumed to be the corresponding dose line.

Additionally, the treatment planning dose has known limitations in that it does not capture all of the effects of protons passing through matter, such as multiple Coulomb scattering. More accurate MC simulations of dose distributions show differences to the planned dose up to $\pm 2.5\%$ of the range in localized areas [1]. A comparison of MC-dose to PET would likely provide better results, but would defeat the purpose of avoiding lengthy MC simulations. Also, the vital information to gather is how much the final delivery deviates from the original treatment plan, and whether that amount necessitates changes to either the plan or the delivery. Thus, comparing the PET to the treatment plan directly avoids ignoring inconsistencies between the plan and the MC simulations that occur when comparing PET to MC-PET.

Comparing PET signal directly to dose has the advantage of avoiding the complexity of Geant4 MC simulations, which are slow, rely on imperfect nuclear production cross sections, and depend on imprecise tissue typing from CT numbers that can affect both the range and activity concentrations. The simple comparison of dose to PET presented here does rely on CT numbers for the standardization, but that has a smaller effect on range.

So far, few studies have analyzed the full cross section of the activated region to determine range differences for the entire area of the beam. Part of the difficulty of comprehensive profile comparisons is the “blind” nature of comparing ranges over the complete beam cross-section. A typical dose might cover an area of 40×40 pixels, or 3600 line profiles, many more than can be assessed individually. The irregular nature of the profiles makes it difficult to define a universal metric for the endpoints. In clinical practice, areas that appear

problematic in the distal surface difference map need to be examined more closely to evaluate the true nature of the discrepancy.

For instance, the results from patient E shows several areas where the range difference is greater than the prescribed 5 mm safety margin (overshoot) and less than -5 mm (undershoot). However, when looking at individual profiles the under/overshoot is less apparent. Patient E is a case where the initial dose-PET comparison should lead to a more indepth analysis. There are also a few areas for patients A, D and F that exceed the safety margins. Fig. 8 shows maps for patients A and D that highlight only areas exceeding the safety margin (i.e., 3.5% of dose range +1 mm). The colored areas would require investigation. In addition, it will be important to determine a method of estimating the uncertainty in the calculated range difference and factor it into any decisions.

After identifying potentially problematic areas there will need to be a determination of whether the range deviation is significant. At a minimum, any areas where the range difference leads to an under-dose (e.g. < 80% of the prescribed dose) to the tumor, or overdose to a critical structure will need to be reviewed. Initially, a human examination of the profiles or other comparison methods must be performed to determine that the range difference is not due to problems with the range difference calculation itself. If it is not, then the plan or delivery may need to be altered. In terms of clinical feasibility, a method such as the one presented here, that can deliver at least preliminary results quickly, will be valuable. Any verified discrepancies between planned and delivered treatments can be addressed and corrected before the next treatment fraction.

The method proposed here does not result in millimeter accuracy, except in very homogeneous cases. Those patients where the beam passes through a more heterogeneous volume of tissue, often including nasal cavities, tend to have more variation in the difference between the dose and simPET distal surfaces and are more difficult to assess. The accuracy here, assuming PET data on par with the simPET, can be derived from the mean standard deviations of the range difference maps, around 3 mm. With PET image quality currently attainable, the accuracy will be closer to 4 or 5 mm. Although it is not millimeter accuracy, it is sufficient for identifying ranges outside of the safety margins on a localized level.

For this method to be useful with PET data, there must be excellent co-registration accuracy between the PET activity, treatment plan dose, and the CT used for attenuation and heterogeneity corrections. An integrated mobile NeuroPET/CT [34] currently in development will provide sufficient sensitivity, spatial resolution (2.5 mm), co-registration accuracy and in-room capabilities to apply this method to measured PET data. In addition, dual-energy CT, possible with the new scanner, can provide better tissue typing for the standardization step [35].

In this feasibility study, we also assumed that a reasonable biological washout model is available so that all of the activity profiles can be “standardized” to similar shapes. However, the washout model currently used by the proton community was adopted from carbon beam studies [26] and its applicability to proton therapy is questionable. A more accurate washout model specifically for proton induced PET activity is very desirable. We are currently developing a new kinetic modeling approach to estimate the ^{15}O production map from dynamic PET data directly. This approach, if successful, is expected to greatly improve the performance of the direct range comparison, since no further reverse washout correction would be necessary.

If PET range verification is to be used routinely in clinics, this simplified approach can serve as an expeditious screening method to filter out cases in need of more time-consuming Monte Carlo analysis. Plotting the distal surface difference between PET and dose presents a

quick view of areas where the dose “undershoots” or “overshoots” the desired location. Those areas around sensitive locations, or with less than full coverage of the tumor, can then be addressed in more detail.

V. Conclusions

We developed a simplified approach for proton range verification with PET by comparing the dose and PET activity end-points directly, and validated our methods with MC simulated patient studies. This new method can adequately detect deliveries where the beam exceeds the safety margins, on a global and local level. It can be used as an expeditious screening method to filter out cases in need of further investigation.

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Fig. 1. Profiles of the dose, MC-PET, and PET activity for a line of voxels along the beam direction in a water phantom [17].

Fig. 2.

Example of the standardization procedure (a) and the water equivalent modulation (b).

Starting from the simulated PET, the reverse decay is applied to the profile, followed by the target density correction (“Standardized”). That standardized profile, along with the dose, is then modulated to a water equivalent range.

(a)

(b)

(c)

(d)

Fig. 3.

Normalized profiles of dose (a) and simPET (b) in a simulated tissue phantom for different modulations of the dose. Lower plots show the details of the upper plots in the distal region, with marks for the 20–50% endpoint (dose) and the linear fit (PET) [17].

Fig. 4.

Dose (a) and simPET (b) distributions for patient A fused with CT, and profiles along the white arrows (c). Endpoints for simPET and dose are indicated with vertical lines. With the systematic correction, the endpoint difference for this profile is less than 1 mm [17].

Fig. 5.

The distal surface differences—range of the dose between 20% and 50% max subtracted from range of the MC-PET from the linear fit—are shown for patients A through F along with histograms of the differences in the ranges. Color scale is in millimeters.

Fig. 6. Range difference maps for patient D, without (a) and with (b) CT modification filling in part of the sinus. CT modified region is circled in green, highlighting the region of undershoot for the filled sinus.

(a)

(b)

(c)

(d)

Fig. 7. Distal surface difference maps and corresponding histograms for the rabbit thigh irradiation. Top: simPET map (a) and histogram (b). Bottom: PET measurement map (c) and histogram (d). The color scale is in millimeters.

Fig. 8.
Range difference maps with all parts masked except those that exceed the safety margins for patient A (a) and patient D (b).

Table 1

Nuclear interaction production of PET isotopes

Interaction	Threshold (MeV)	Half-life (min)
$^{16}\text{O}(\text{p,pn})^{15}\text{O}$	16.79	2.037
$^{16}\text{O}(\text{p},2\text{p}2\text{n})^{13}\text{N}$	5.66	9.965
$^{14}\text{N}(\text{p,pn})^{13}\text{N}$	11.44	9.965
$^{12}\text{C}(\text{p,pn})^{11}\text{C}$	20.61	20.39
$^{14}\text{N}(\text{p},2\text{p}2\text{n})^{11}\text{C}$	3.22	20.39
$^{16}\text{O}(\text{p},3\text{p}3\text{n})^{11}\text{C}$	27.5	20.39
$^{31}\text{P}(\text{p,pn})^{30}\text{P}$	19.6	2.498
$^{40}\text{Ca}(\text{p},2\text{pn})^{38}\text{K}$	21.2	7.636

Table II

Mean and standard deviation of the distal surface differences between dose and simPET for the six patients

Patient	Mean difference (mm)	Std. dev. (mm)
A	-1.6	1.9
B	0.5	1.6
C	-0.4	1.1
D	0.4	2.7
E	-0.9	4.0
F	-1.7	2.5