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Mapping ^{15}O production rate for proton therapy verification

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Abstract

Purpose—This is a proof-of-principle study for the evaluation of ^{15}O production as an imaging target, through the use of positron emission tomography (PET), to improve verification of proton treatment plans and study the effects of perfusion.

Methods and Materials—Dynamic PET measurements of irradiation-produced isotopes were taken for a phantom and rabbit thigh muscles. The rabbit muscle was irradiated and imaged in both live and dead conditions. A differential equation was fitted to the phantom and the *in vivo* data, yielding estimates of the ^{15}O production and clearance rates, which was compared for live versus dead for the rabbit, and to Monte Carlo (MC) predictions.

Results—PET clearance rates agreed with the decay constants of the dominant radionuclide species in three different phantom materials. In two oxygen-rich materials, the ratio of ^{15}O production rates agreed with the MC prediction. In the dead rabbit thighs, the dynamic PET concentration histories were accurately described using the ^{15}O decay constant, while the live thigh activity decayed faster. Most importantly, the ^{15}O production rates agreed within 2% ($p > 0.5$) between conditions.

Conclusion—We developed a new method for quantitative measurement of ^{15}O production and clearance rates in the period immediately following proton therapy. Measurements in the phantom and rabbits were well described in terms of ^{15}O production and clearance rates, plus a correction for other isotopes. These proof-of-principle results support the feasibility of detailed verification

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of proton therapy treatment delivery. In addition, ^{15}O clearance rates may be useful in monitoring permeability changes due to therapy.

INTRODUCTION

High energy proton beams deposit the highest dose near the end of the path (the Bragg peak). Because of large dose gradients near the Bragg peak, proton range inaccuracy is of concern, especially when there is a critical structure lying distal to the target volume (1). During proton therapy, positron emitting radionuclides, such as ^{15}O , ^{13}N and ^{11}C , are produced through nuclear fragmentation reactions, and PET imaging of the activity distribution of these proton-induced positron emitters has emerged as a practical approach for *in vivo* proton therapy range verification. Various methods using PET imaging are being investigated in several institutions around the world (2–11).

The spatial distribution of the produced positron emitters is related to proton fluence, nuclear reaction cross-sections, and target nuclide concentration distributions. Therefore, the PET activity differs from the dose distribution (4, 12). Because the PET activity distribution is not shaped like the dose distribution, verification of the treatment plan and beam delivery relies on Monte Carlo (MC) predictions to connect the dose to the three-dimensional distribution of PET-measured radioactivity concentration. The limitation of this method is that MC simulations assume radioactivity simply builds up in the tissue due to proton irradiation. Previous work used a washout model, including nominal values for biological clearance, which were applied to the MC data retrospectively (2, 13). Simulations were used to generate predictions of the production rates of the positron emitters using treatment planning information and tissue composition maps (14) obtained from CT images. Thresholds on the treatment-CT image numbers were set to identify fat, soft tissue, bone, cortical bone, muscle, and brain tissues. The washout in each tissue type was decomposed into three components—fast, medium and slow—as described by Parodi, et al. (13). Fractions and biological half-lives were assigned to each tissue type, based on animal study results with stable and radioactive carbon ion beams. After applying radioactive and biological decay corrections, distributions from different radionuclides were summed to form the predicted PET activity distributions and compared with static PET images (2). This model has several limitations: The parameters were adopted from carbon-beam studies (15) whose applicability to proton beam therapy is questionable (16), as projectile fragmentation is more important in carbon ion therapy, while only target fragmentation is possible in proton therapy (4). In addition, the previous model-correction method does not account for varied washout rates of radionuclides incorporated as different molecules. In fact, the CT number is insufficient to fully characterize the tissue environment; the chemical form of the product determines its biological fate. In addition, biological clearance rate is greatly affected by the prevailing biological environment, such as local vascular development, tissue heterogeneity and perfusion rate, not to mention prior chemotherapy or radiation treatment. Clinical studies have shown that biological washout was one of the major reasons for the discrepancies between the measured and simulated ranges when the proton beam stops in soft tissue (17).

This paper introduces a novel and innovative method designed to overcome the limitations discussed above, suitable for measuring the production and clearance rate of ^{15}O in individual subjects. The production rate map (the distribution of total activity produced during irradiation) can be estimated voxel-by-voxel from dynamic PET reconstructions, before comparison to MC prediction. Previous approaches to this problem focused on just the clearance of radionuclides. However, the measured concentration can be seen as a balance between build-up due to irradiation, and clearance due to both radioactive decay and biological elimination. The parameter of greatest interest is the production rate, but the clearance rate may also prove valuable in monitoring changes in the tissue environment due to treatment. As a proof of concept, we describe the rationale for the model, and the validation of the approach with phantom and animal studies.

Our long-term goal is to verify proton therapy delivery by comparing the PET-measured and Monte Carlo (MC)-predicted local production rate of ^{15}O produced in tissue during proton irradiations. To that end, this paper investigates three ideas: (1) Application of conservation laws to connect the time rate of change in the PET-measured radioactivity concentration as the difference between the isotope production rate, and clearance due to radioactive decay and biological elimination. (2) Immediately after proton irradiation the PET signal is predominantly due to ^{15}O production, meaning that clearance curves can be described as the clearance of ^{15}O -labeled H_2O , with a correction for longer-lived products. (3) Dynamic PET measurements taken soon after irradiation (in-beam or in-room) can be used to measure both the production and clearance rates.

METHODS AND MATERIALS

A kinetic model for the production and clearance of PET activity

The radionuclides produced from the nuclear fragmentation reactions (^{15}O -, ^{13}N - and ^{11}C , etc.) are initially in the free ion form but soon, typically within milliseconds, combine with a nearby ion/molecule to form a new molecule. The labeled molecule will be eliminated from the reaction volume by two mechanisms, radioactive decay and biological washout. The activity concentration of the i^{th} labeled molecule, C_i , can be described with the following equation:

$$\frac{dC_i}{dt} = R_0(t) - k_i C_i, \quad (1)$$

where $R_0(t) = \begin{cases} R_i, & t < T \\ 0, & t \geq T \end{cases}$ is the (constant) activity production rate, T is the irradiation duration, and k_i is the combined clearance rate of the i^{th} molecular species:

$$k_i = \lambda_{ia} + \lambda_{ib}, \quad (2)$$

where λ_{ia} is the radioactive decay constant, and λ_{ib} is the biological washout rate. Note that one radionuclide, when labeled on different molecules, would have the same radioactive decay constant but different biological clearance rate. This formulation assumes a cyclotron beam delivery of a passively scattered proton treatment. Synchrotron beams and beam

scanning would require modifications based on delivery timing parameters. Solving equation (1), the total activity concentration at time t will be the sum of all molecules containing proton-induced radionuclides:

$$A(t) = \sum_i C_i(t) = \begin{cases} \sum_i \frac{R_i}{k_i} (1 - e^{-k_i t}), & t < T \\ \sum_i \frac{R_i}{k_i} (e^{k_i T} - 1) e^{-k_i t}, & t \geq T \end{cases} \quad (3)$$

In theory, R_i and k_i can be determined by fitting the time course of activity concentration (obtained from dynamic PET reconstructions) with equation (3) using a least-square approach. In practice, to account for imaging duration, the time average of the model prediction is used in equation (3). In this case, C_i for the $t = T$ case should be substituted with

$$C'_i(T_0) = \frac{1}{T_{frame}} \int_{T_0}^{T_0 + T_{frame}} \frac{R_i}{k_i} (e^{k_i T} - 1) e^{-k_i T} dt = \frac{(e^{k_i T} - 1)}{k_i T} \frac{(1 - e^{-k_i T_{frame}})}{k_i T_{frame}} (R_i \cdot T) e^{-k_i T_0} \quad (4)$$

where T_0 is the starting point of the image frame relative to the start of irradiation and T_{frame} is the imaging frame length.

In reality, it is impossible to obtain the exact compositions of the labeled-molecule cocktail in equation (4), and fit for them all, because of image noise and the finite measurement period of the time-activity history. However, it has been shown (18, 19) that ^{15}O contributes to over 80% of PET signal for the first few minutes after treatment. Because of the high water content in the human body, it is highly likely that ^{15}O will form into ^{15}O -labeled water molecules. With this observation/assumption, we fit the dynamic data with one component representing ^{15}O -H₂O (parameters R_1 and k_1), and another correction term representing other longer half-life labeled-molecules (R_2 and k_2). A three-dimensional R_1 map is obtained by fitting the proton activated volume voxel-by-voxel, which can be compared with MC-predictions for treatment verification.

Validation with phantom study

An in-house made phantom was used for the phantom study. It contained three materials: high-density polyethylene (HDPE), gelatinous water (water-gel) and tissue equivalent gel (tissue-gel). The purpose was to measure the proton activation in carbon-rich, oxygen-rich and tissue-like (realistic carbon/oxygen ratio) materials in parallel. The phantom construction and material properties are shown in Fig. 1.

The phantom was irradiated with a square $7 \times 7 \text{ cm}^2$, 2-Gy spread-out Bragg-peak (SOBP) passively scattered field with a 10-cm water-equivalent (WE) range and a 6-cm WE modulation for 39 seconds. After a 51-second delay, the phantom was imaged in a mobile NeuroPET scanner (PhotoDiagnostic Systems, Inc., PDSi) for 30 minutes in list-mode. The list-mode PET data were reconstructed into 1-minute dynamic frames. The predicted ^{15}O production rate map was calculated with MC simulations, as described elsewhere (18), and smoothed with a 4.6-mm 3-D Gaussian filter to account for the finite spatial resolution of the NeuroPET scanner (4.3 mm) and the positron range of ^{15}O ($\sim 1.5 \text{ mm}$ FWHM in water).

In phantom studies, without the presence of biological washout, the expected model-estimated clearance rate is the decay constant (i.e., $k = \lambda_a$) of the dominant radionuclide. Dynamic data were fitted with the kinetic model to test if it correctly estimates the decay constants of ^{11}C (HDPE) and ^{15}O (water and tissue gels). We also tested if the model correctly estimates the ratio of ^{15}O production rates for the two oxygen-rich materials, water-gel and tissue-gel.

Activity concentrations in a large region of interest (ROI) in each material were used to generate time-activity curves (TACs) with low noise. The TACs were fitted with the model to estimate the production and clearance rates of ^{15}O . The activated volume was also fit voxel-by-voxel to generate the ^{15}O production rate (R_I) map. The estimated R_I maps and ^{15}O activity production profiles along the beam path were compared with MC predictions from the Geant4-based program TOPAS (20).

In Vivo Validation

The thigh muscle of a New Zealand White rabbit was irradiated twice, once in the live (perfused) condition and once immediately after sacrificing, in the non-perfused condition, to test two predictions: (1) The ^{15}O production rates will be the same in the live and dead conditions; and (2) the initial clearance rate, k_I , for the dead condition will be equal to the decay constant for ^{15}O . A 5 Gy SOBP field with range 5 cm and modulation 2 cm was delivered in 268 seconds for each condition, followed by list-mode PET acquisition in a NeuroPET/CT. A second rabbit thigh was irradiated and scanned with a similar protocol, but with a shorter delivery time, $T = 54$ seconds, and with the beam passing through the whole thigh for less uncertainty in co-registration between live and dead conditions.

The dynamic data in an ROI in the irradiated muscle in the first rabbit, and an ROI in a bony region in the second rabbit, were fit with the model to determine the ^{15}O production and clearance rates. For the dead, non-perfused, condition, the total clearance rate was compared to the decay constant of ^{15}O . The model-estimated ^{15}O production rates for the two conditions were compared with each other by Student's t-test. The irradiated region for the second rabbit was also fitted voxel-by-voxel for both conditions.

All animal procedures were conducted in accordance with the regulations of the XXXX Animal Care and Use Committee.

RESULTS

Model validation with the phantom study

HDPE (high-density polyethylene)—The fitted curves for HDPE (C_2H_4) are shown in Figs. 2a. The slight rise of time-activity curve at the beginning is from the ^{10}C from the $^{12}\text{C}(\text{p}, \text{p}2\text{n})^{10}\text{C}$ reaction channel, which has a half-life of 19 sec. Skipping the first 10 time points and fitting the rest with one k-parameter (when the contribution of ^{10}C can be ignored), the k value ($k_I = 0.0351 \pm 0.0004 \text{ minute}^{-1}$) was very close to the k_2 in the 2-parameter case, and in good agreement with the ^{11}C decay constant.

Tissue-equivalent gel and water gel, containing O, C, N and H—All time points from the tissue-gel and water-gel ROIs were first fit with two k-parameters to test if the Eq. 4 model can correctly predict the decay constants. See Fig. 2(a) for the data and fit result. For both materials, k_1 agreed within 3% with the decay constant of ^{15}O : $k_1 = 0.339 \pm 0.004 \text{ minute}^{-1}$ for tissue gel, $0.336 \pm 0.003 \text{ minute}^{-1}$ for water gel, compared to ^{15}O decay constant of $0.3402 \text{ minute}^{-1}$. The k_2 's were $0.0390 \pm 0.0012 \text{ minute}^{-1}$ for tissue gel and $0.0396 \pm 0.0024 \text{ minute}^{-1}$ for water gel, both between the decay constants of ^{11}C ($0.0340 \text{ minute}^{-1}$) and ^{13}N ($0.0696 \text{ minute}^{-1}$). The ratio of production rates (R_1 's) for the water and tissue gels was 1.06 ± 0.03 , in agreement with expectation. Given that the only mode of ^{15}O production is from $^{16}\text{O}(\text{p,pn})^{15}\text{O}$, the expected ratio of ^{15}O production rates in the two materials is 1.06, based on the relative oxygen content (87.6% and 73.8% for water-gel and tissue-gel, respectively) and the densities (1.01 and 1.13 g/cc).

Volume fitting with the phantom study

The activated volume in the second phantom study was fitted voxel-by-voxel to generate the ^{15}O production rate (R_1) map. The voxel size was $2 \times 2 \times 1.925 \text{ mm}^3$ (the original PET image grid). In all the fittings, the k_2 parameter was pre-set to $0.039 \text{ minute}^{-1}$. The fitting results for Eq. 4 to one slice are compared with MC predictions in Figs. 2(b)–2(d). The oxygen-rich tissue-gel regions can be clearly distinguished from the low-oxygen HDPE region.

The activity production profiles in the tissue gel along the beam path (indicated by the red vertical lines in the images in Figs. 2(c) and (d)) are shown in Fig. 2(b). The model estimated and MC predicted activity profiles have the same shape. The 10% discrepancy in absolute quantitation may be attributed to miscalibration of the scanner and uncertainties in cross sections used in the MC simulations, as indicated in (18, 21).

Model validation with the animal study

Fig. 3(a) shows sample PET images of the live (perfused) and dead (non-perfused) rabbit thigh fused with CT. Fig. 3(b) shows the fitted time-activity curve of the muscle ROI measured in both conditions. The first 15 time points (15-minutes of PET) were fitted with a k_2 lower bound of 0.039 min^{-1} , based on the tissue phantom results. The model-estimated clearance rate in a region of interest was $0.349 \pm 0.005 \text{ minute}^{-1}$, in excellent agreement with the ^{15}O decay constant. The live clearance rate was estimated to be 0.396 ± 0.023 , greater than the dead clearance rate (one tailed t-test, $p=0.1$), and giving a biological decay constant of $0.049 \pm 0.02 \text{ minute}^{-1}$.

For the bony ROI in the second rabbit, $k_1 = 0.34 \pm 0.02 \text{ minute}^{-1}$ for the dead case, in agreement with the ^{15}O decay constant, and $0.37 \pm 0.01 \text{ minute}^{-1}$ for live case, giving a biological decay constant of $0.028 \pm 0.02 \text{ minute}^{-1}$. The biological decay for the bony region is slower, given bone has lower perfusion.

The model-estimated ^{15}O production rate in the muscle ROI during irradiation was $98 \pm 1 \text{ Bq/ml/s}$ for the dead condition and $101 \pm 3 \text{ Bq/ml/s}$ for the live condition, differing by $2 \pm 4\%$ ($p>0.5$). We also performed a joint fitting of the live and dead curves, constraining both

R-values to be the same. We found $R_1 = 99 \pm 2$ Bq/ml/s, in excellent agreement with the separate fit. The slight deviation at later times for the live case is likely an effect of combining the other PET isotopes (^{11}C and ^{13}N) into one correction factor. The MC estimated production rate for the same ROI was 87 ± 1 Bq/ml/s. For the bony region of the second rabbit, the ^{15}O production rates were in excellent agreement ($p > 0.5$): 239 ± 5 and 240 ± 6 Bq/ml/s for live and dead, respectively. The model was also applied to an ROI in the muscle of the same rabbit, adjacent to the bony ROI. The production rates were 261 ± 1 and 263 ± 2 for live and dead. The ratio of production rates in muscle and bone was 1.08 ± 0.03 , in agreement with the material composition ratio of 1.08 ± 0.01 . The tissue composition was based on density and oxygen content determined from the CT scan, according to the method outlined by Schneider *et al.* (14).

One slice of the fitted ^{15}O production rate map for the live and dead conditions in the second rabbit is shown in Fig. 4(a). The activity production profiles along the beam path are shown in Fig. 4(b). The profiles for the live and dead conditions have a very similar shape. Some of the differences in amplitude are attributed to changes in muscle tone occurring after sacrifice. None of the standard-error-weighted differences between the two maps exceed the threshold calculated based on Gaussian random fields theory for multiple comparisons in correlated images (22, 23).

DISCUSSION

Proton-induced PET activity distributions can be compared to MC predictions, based on the treatment plan, to determine deviations in the intended dose range. However, biological washout complicates the radioactivity imaged because the image intensities cannot be relied upon to discriminate biological clearance from absence of deposition. Biological clearance can dramatically change the original proton-induced activity distribution, particularly in soft tissue. Our previous corrections for biological clearance were applied directly to the Monte Carlo prediction of the activity and thus could not fully account for subject-to-subject variability. In this paper we have proposed a new endpoint, the ^{15}O -production rate. By using dynamic PET measurements we can estimate both the ^{15}O production rate and the clearance rate of water. The advantage of this approach is that we can compare the MC prediction directly with the PET measurement. We expect future development of this comparison to allow the MC prediction of ^{15}O -production thresholds to quantify beam range measurements.

In theory, by fitting the proton activated volume voxel-by-voxel, we will obtain a three-dimensional R_1 map, which can be compared with a MC-predicted R_1 map for treatment verification. The results suggest it is feasible to obtain the original ^{15}O distribution from dynamic reconstruction data, provided that the data is taken within 3–4 minutes of irradiation, to ensure a high proportion of ^{15}O activity. The production rate can be recovered with 10–15 minutes of PET acquisition in phantom and animal studies. With in-beam imaging it is likely that the acquisition can be reduced to 5 minutes, given the dramatic increase in statistics. Remaining discrepancy between the MC and PET predicted production rates in the rabbit study might be attributed to uncertainties in the cross-sections, the image registration, and CT numbers used in the MC calculation. More importantly, the same R_1

value was recovered for both live and dead conditions in both rabbits for the same irradiations, indicating that the model can correct for biological clearance effects. It has been shown to work in both muscle (~70% oxygen) and bone (~45% oxygen). Adipose tissue, with ~25% oxygen content, has not yet been tested. However, most irradiation sites will not have an abundance of fat except for the beam entrance region (subcutaneous fat layer). Furthermore, both bone and fat are poorly perfused, leading to more signal and smaller corrections due to biological washout.

For future work, we will implement our method with 3-D volumes from patient images taken shortly after standard treatment. We will compare the volumetric R_1 maps to those estimated by MC-simulations. In particular, we will compare the expected and measured ranges between the two to identify deviations and relate those back to differences in the intended treatment.

In addition to the ^{15}O production rate map, our method produces a map of the water clearance rate, which can potentially be used for the evaluation of tumor response to therapy during fractionated treatments. The washout pattern of proton-produced activity is related to perfusion and the biological environment of tumors and tissues, such as local vasculature and local changes in the permeability of water. After several treatments, the tumor perfusion and/or permeability may change in response to the therapy. These changes in washout patterns could carry useful biological information that can be used to individualize therapy to optimize treatment response.

The new method proposed in this paper is based on well-established principles – the conservation of tracer mass and the compartment modeling of the clearance of labeled water. We have presented a general theory, applicable to time epochs during or shortly (~2–3 minutes) following treatment. Further analysis suggests that there is significant advantage to imaging when the dynamic PET data can be represented as the clearance of water, with nominal correction for ^{11}C -labeled molecules. Due to the biochemistry of carbon, it is likely that ^{11}C is incorporated into many molecules with varying clearance rates. The observed mixtures of ^{11}C compounds will change depending on exactly when the measurements commence. Rapidly clearing ^{11}C -compounds may not be measured, leading to errors in the ^{11}C production rate.

In summary, we have provided a novel method for the measurement of ^{15}O production and clearance that is potentially suitable for verifying the treatment delivery in patients undergoing proton beam therapy.

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Fig. 1.
Phantom used for the study, with material compositions.

Fig. 2. Phantom study results. (a) Fitted TACs of three materials. (b) Model estimated and MC predicted sample ^{15}O production rate profile in tissue gel. (c) Example PET images of the first and fifth time frames. (d) Example MC predicted and our model predicted ^{15}O production rate maps. The red vertical lines indicate the position of the activity profile shown in (b).

Fig. 3. Rabbit study results. (a) Dead and live PET images overlaid on the CT scan, with beam direction and ROI indicated in cyan. (b) The time activity data from the ROI. The lines are the model predictions for the experimental period and the concentration during irradiation.

Fig. 4. Slice from the 3D production rate (R_1) maps, overlaid on the CTs. for (a) live and (b) dead second rabbit. (c) Profile through the activity map corresponding to the line indicated on the maps.