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Determination of elemental tissue composition following proton treatment using positron emission tomography

Jongmin Cho¹, Geoffrey Ibbott¹, Michael Gillin¹, Carlos Gonzalez-Lepera², Chul Hee Min³, Harald Paganetti⁴, Xuping Zhu⁴, Georges El Fakhri⁴, and Osama Mawlawi⁵

¹Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

²Department of Experimental Diagnostic Imaging, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

³Department of Radiological Science, College of Health Science, Yonsei University, Wonju, Kangwon-Do, 220–710, Republic of Korea

⁴Departments of Radiation Oncology and Radiology, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114, USA

⁵Department of Imaging Physics, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

Abstract

Purpose—Positron emission tomography (PET) has been suggested as an imaging technique for *in vivo* proton dose and range verification after proton induced-tissue activation. During proton treatment, irradiated tissue is activated and decays while emitting positrons. In this paper, we assessed the feasibility of using PET imaging after proton treatment to determine tissue elemental composition by evaluating the resultant composite decay curve of activated tissue.

Methods—A phantom consisting of sections composed of different combinations of ¹H, ¹²C, ¹⁴N, and ¹⁶O was irradiated using a pristine Bragg peak and a 6-cm spread-out Bragg-peak (SOBP) proton beam. The beam ranges defined at 90% distal dose were 10 cm; the delivered dose was 1.6 Gy for the near monoenergetic beam and 2 Gy for the SOBP beam. After irradiation, activated phantom decay was measured using an in-room PET scanner for 30 minutes in list mode. Decay curves from the activated ¹²C and ¹⁶O sections were first decomposed into multiple simple exponential decay curves, each curve corresponding to a constituent radioisotope, using a least-squares method. The relative radioisotope fractions from each section were determined. These fractions were used to guide the decay curve decomposition from the section consisting mainly of ¹²C+¹⁶O and calculate the relative elemental composition of ¹²C and ¹⁶O. A Monte Carlo simulation was also used to determine the elemental composition of the ¹²C + ¹⁶O section. The calculated compositions of the ¹²C + ¹⁶O section using both approaches (PET and Monte Carlo) were compared with the true known phantom composition. Finally, 2 patients were imaged using an in-room PET scanner after proton therapy of the head. Their PET data and the technique described above were used to construct elemental composition (¹²C and ¹⁶O) maps that corresponded to the proton-activated regions. We compared the ¹²C and ¹⁶O compositions of 7 ROIs that corresponded to the vitreous humor, adipose/face mask, adipose tissue, and brain tissue with ICRU 46 elemental composition data.

Results—The ^{12}C and ^{16}O compositions of the $^{12}\text{C} + ^{16}\text{O}$ phantom section were estimated to within a maximum difference of 3.6% for the near monoenergetic and SOBP beams over an 8-cm depth range. On the other hand, the Monte Carlo simulation estimated the corresponding ^{12}C and ^{16}O compositions in the $^{12}\text{C} + ^{16}\text{O}$ section to within a maximum difference of 3.4%. For the patients, the ^{12}C and ^{16}O compositions in the 7 ROIs agreed with the ICRU elemental composition data, with a mean (maximum) difference of 9.4% (15.2%).

Conclusions—The ^{12}C and ^{16}O compositions of the phantom and patients were estimated with relatively small differences. PET imaging may be useful for determining the tissue elemental composition and thereby improving proton treatment planning and verification.

Keywords

Proton therapy; positron emission tomography (PET); treatment verification; elemental composition; tissue composition; Monte Carlo simulation; radioactive decay

1. Introduction

Proton therapy is increasingly gaining acceptance in cancer treatment. Currently, 10 proton therapy centers operate in the United States, and a similar number will become operational by 2020 (<http://www.proton-therapy.org/>). The power of proton therapy is that the maximum radiation dose (at the Bragg peak) is deposited just before the end of the proton path; beyond this point, the dose quickly falls to zero. This characteristic enables proton beams to deliver large radiation doses to tumors while sparing critical distal organs. For ideal proton treatment outcomes, an accurate calculation of tissue stopping power is needed to estimate the proton beam's dose and range. According to the Bethe formula, an accurate calculation requires 2 patient-specific inputs—tissue electron density and elemental composition information. Tissue electron density can be obtained from CT images, but currently there are no imaging techniques that can provide tissue elemental composition. Calculating tissue stopping power based on electron density alone has been suggested to result in 2% or higher (when including tissue heterogeneity) uncertainty (Paganetti 2012). This uncertainty in tissue results in > 3.5% proton range uncertainty when other confounding factors such as CT calibration differences and energy dependence are taken into consideration (Mustafa and Jackson 1983, Alpen *et al* 1985, Moyers *et al* 2010). Furthermore, Jiang *et al* 2007 found that using CT number conversion associated with inaccurate tissue elemental composition assignments, leads to significant errors in determining the proton range. Moyers *et al* 2010 also found that the calculated CT number (from calculated relative attenuation coefficient (Mustafa and Jackson 1983)) of certain materials can differ up to 49% from their true CT numbers when their exact elemental compositions are unknown. On the other hand, when the elemental composition was known these differences were reduced to $\pm 4\%$ (Moyers *et al* 2010). Collectively these findings suggest that uncertainty in elemental compositions can give rise to additional uncertainty in stopping power calculations and therefore lead to more uncertainties in proton dose and range.

To overcome these uncertainties, positron emission tomography (PET) has been suggested for *in vivo* proton dose and range verification after proton tissue activation (Paans and Schippers 1993, Oelfke *et al* 1996, Litzenberg *et al* 1999, Nishio *et al* 2005, Crespo *et al* 2006, Parodi *et al* 2007a, 2007b, Knopf *et al* 2008). During proton treatment, irradiated tissue is activated and decays among other schemes by positron emission, which subsequently results in annihilation photons that can be imaged using a PET scanner. Proton dose and range verification can be realized by correlating tissue activation with dose deposition. However, accurate knowledge of the tissue's elemental composition is essential

for correlating activation with dose (Parodi *et al* 2007b, Knopf *et al* 2009, Knopf *et al* 2011, España *et al* 2011). Depending on the underlying geometrical homogeneity, proton dose deposition in tissue can be insensitive to the normal variations in tissue elemental composition (Paganetti 2012), but proton tissue activation and its measurement by PET is quite sensitive. For example, 2 adjacent regions with different tissue elemental compositions can have different activation signal intensities, even though they were irradiated by the same proton spectrum and dose; this is because dose deposition and activity originate from two different physical processes. España and Paganetti, 2010 have demonstrated that Monte Carlo simulated PET is more sensitive than Monte Carlo simulated dose using different CT conversion algorithms. Thus, it is impossible to accurately correlate the delivered dose with the activated tissue extent without correct elemental composition information about the irradiated tissue.

In this study, we investigated whether PET imaging can be used to determine tissue elemental composition in patients who have undergone proton therapy. If successful, we envision that after the first proton treatment fraction, patients will be able to undergo PET scanning with an in-room PET scanner. The tissue elemental composition information can be used to verify and potentially correct the original proton treatment plan, which had been based on a Hounsfield Unit to stopping power conversion curve. We also envision that conventional proton treatment verification using PET can be improved by providing tissue elemental composition information. By normalizing tissue PET signals with the correct tissue elemental composition information, more accurate correlation between the PET signal and the delivered dose becomes possible. To our knowledge, this work is the first to use PET to analyze patients' tissue elemental composition.

2. Materials and Methods

2.1 Phantom Activation and PET Imaging

A phantom consisting of three 12-cm long sections that were composed of high-density polyethylene (HDPE), water gel, and tissue gel, respectively, was proton irradiated at the Francis H. Burr Proton Therapy Center (Massachusetts General Hospital, Boston, MA). The phantom and corresponding elemental composition fractions are shown in figure 1 and table 1, respectively. Because HDPE, water gel, and tissue gel consist mostly of ^{12}C , ^{16}O , and a mixture of ^{12}C and ^{16}O , respectively, they will be hereafter referred to as ^{12}C phantom, ^{16}O phantom, and $^{12}\text{C}+^{16}\text{O}$ phantom, respectively. The composite phantom was activated using two 116-MeV proton beams—a pristine Bragg peak and a 6-cm spread-out Bragg peak (SOBP) beam. The time interval between the 2 beams was 2 hours. A square field of 7×7 cm was used to irradiate the phantom, as shown in figure 1. Within 1 minute after each proton activation, the phantoms were moved to a mobile PET scanner (NeuroPET, Photo Diagnostic Systems, Boxboro, MA) that was placed immediately adjacent to the treatment couch and imaged for 30 minutes in list mode. PET data were then sorted into 30 1-minute data sets and reconstructed with no decay correction. The reconstructed PET voxels were $2\times 2\times 1.925$ mm. Volumes of interest (VOIs) of $2\times 2\times 1$ cm were then drawn on each phantom section at 1-cm water equivalent thickness intervals and the PET signal from every VOI was averaged. The details of the PET data acquisition and of the reconstruction are discussed in España *et al* 2011.

The irradiated phantoms create multiple positron-emitting radioisotopes. for example, ^{16}O atoms create ^{11}C , ^{13}N , and ^{15}O isotopes after proton irradiation. When a sample with T atoms in voxel r and density $\rho_T(r)$ is irradiated using a proton beam with a fluence of $E(r,t)$, each resulting isotope I is created according to its isotope production cross section, $\sigma_{TI}(E(r))$, while simultaneously decaying according to its specific half-life. After irradiation,

the activity from the remaining radioisotopes at time t ($t = 0$ when irradiation was complete) in voxel r is

$$a_i(r, t) = \sum_T \rho_T(r) \Phi^E(r, t) \sigma_{Ti}(E(r)) (1 - e^{-\lambda_i t_R}) e^{-\lambda_i t} \quad (1)$$

where λ_i and t_R are the isotope decay constant and irradiation (beam-on) time, respectively. This formula considers the number of created and decayed atoms of radioisotope i during t_R .

2.2 Method of Decoupling Decay Curves

After proton irradiation, ^{12}C , ^{14}N , and ^{16}O atoms in the composite phantom are activated to several radioisotopes that decay by positron emission. Because HDPE, water gel, and tissue gel consist mostly of ^{12}C and ^{16}O (see table 1), other elements such as ^{14}N in the $^{12}\text{C} + ^{16}\text{O}$ phantom and ^{12}C and ^{14}N in the ^{16}O phantom have low fractions (<2%) and are ignored.

Activation of the ^{12}C phantom creates ^{10}C and ^{11}C ; these simultaneously decay with half-lives of 19.29 seconds and 20.33 minutes, respectively (eq.2). The relative fractions of ^{10}C and ^{11}C radioisotopes is governed by factors such as proton nuclear cross section, proton beam energy and fluence, and proton beam time, as explained in eq. 1. In the same way, the activated ^{16}O phantom creates ^{11}C , ^{13}N , and ^{15}O , which simultaneously decay with half-lives of 20.33 minutes, 9.96 minutes, and 122.24 seconds, respectively (eq.3). Proton interaction channels and nuclear interaction cross sections for ^{12}C and ^{16}O are shown in table 2 and figure 2.

$$\text{Activated } ^{12}\text{C} = \alpha ^{11}\text{C} + \beta ^{10}\text{C} \quad (2)$$

$$\text{Activated } ^{16}\text{O} = \alpha' ^{11}\text{C} + \beta' ^{13}\text{N} + \gamma' ^{15}\text{O} \quad (3)$$

where α , β , α' , β' , γ' are the relative fractions of created radioisotopes. α and β are determined as best-fit parameters when the summation of 2 simple exponential decay curves, with half-lives of 20.33 minutes and 19.29 seconds, is fitted to the PET time activity curve from activated ^{12}C , using a least-square technique (figure 3a). The details of how to separate multiple PET tracers from a single decay curve using the least-squares method can be found in Huang *et al* 1982. In the same way, α' , β' , and γ' can be obtained from the activated ^{16}O phantom (figure 3b). α , β , α' , β' , γ' are depth dependent because proton energy and fluence change with depth and proton nuclear cross sections change with proton energy. Therefore, the above procedure was repeated at 1-cm depth intervals along the length of the phantom to determine the corresponding α , β , α' , β' , and γ' .

Activation of the $^{12}\text{C} + ^{16}\text{O}$ phantom is more complex because it consists of 2 elements. However, the same technique can still be used to determine the elemental composition and fraction of each element. Activating the $^{12}\text{C} + ^{16}\text{O}$ phantom creates the radioisotopes ^{10}C , ^{11}C , ^{13}N , and ^{15}O , with each radioisotope fraction dependent on proton energy, fluence, and amount of ^{12}C and ^{16}O in the $^{12}\text{C} + ^{16}\text{O}$ phantom:

$$\text{Activated } ^{12}\text{C} + ^{16}\text{O} = \alpha'' ^{10}\text{C} + \beta'' ^{11}\text{C} + \gamma'' ^{13}\text{N} + \delta'' ^{15}\text{O} \quad (4)$$

The raw decay curve from the activated $^{12}\text{C} + ^{16}\text{O}$ phantom can be separated into 4 exponentials— α'' , β'' , γ'' , and δ'' —using the method of least-squares, whose summation (fit) agrees with the raw decay curve (figure 4a). This separation alone, however, cannot determine the fraction of ^{12}C and ^{16}O in the $^{12}\text{C} + ^{16}\text{O}$ phantom because β'' is a compound factor that is contributed to by ^{12}C and ^{16}O activation (see eqs. 2 and 3). One approach to

determine the ^{12}C and ^{16}O fraction in the $^{12}\text{C} + ^{16}\text{O}$ phantom is to equate its activation with the sum of ^{12}C and ^{16}O activations. Such a method of determining the fractions of induced isotopes in a mixed target from the activity in pure targets was first described by Priegnitz et al. 2008 and Priegnitz et al. 2012. A similar approach has been also developed by Miyatake et al. 2009 and Miyatake et al. 2011.

$$\text{Activated } ^{12}\text{C} + ^{16}\text{O} = a \text{ activated } ^{12}\text{C} + b \text{ activated } ^{16}\text{O}$$

$$\alpha''^{10}\text{C} + \beta''^{11}\text{C} + \gamma''^{13}\text{N} + \delta''^{15}\text{O} = a(\alpha'^{11}\text{C} + \beta'^{10}\text{C}) + b(\alpha'^{11}\text{C} + \beta'^{13}\text{N} + \gamma'^{15}\text{O}) \quad (5)$$

$$\text{Activated } ^{12}\text{C} + ^{16}\text{O} = a'(^{11}\text{C} + \alpha''^{10}\text{C}) + b'(^{11}\text{C} + \beta''^{13}\text{N} + \gamma''^{15}\text{O}) \quad (6)$$

where a and b are the relative contributions (or fractions) of ^{12}C and ^{16}O , respectively in the activated $^{12}\text{C} + ^{16}\text{O}$ (figure 4b). Here, the factor β'' from eq. 4 has been separated into 2 components, a' and b' (or $a\alpha'$ and $b\alpha'$), which are the ^{11}C contributions from the activated ^{12}C and ^{16}O , respectively. Here $\alpha'' = \beta/\alpha$, $\beta'' = \beta'/\alpha'$, and $\gamma'' = \gamma'/\alpha'$. Because α , β , α' , β' , and γ' (and also α'' , β'' , and γ'') have already been determined at each depth, a' and b' for each depth can be calculated by minimizing the root mean square error between the raw decay curve of the $^{12}\text{C} + ^{16}\text{O}$ phantom and the sum of the best fits of the 2 decay curves of ^{12}C and ^{16}O (eq. 7):

$$\begin{aligned} \text{Least squares to be minimized to obtain } a' \text{ and } b' = & (\text{Activated } ^{12}\text{C} + ^{16}\text{O} - a'(^{11}\text{C} \\ & + \alpha''^{10}\text{C}) \\ & - b'(^{11}\text{C} + \beta''^{13}\text{N} + \gamma''^{15}\text{O}))^2 \end{aligned} \quad (7)$$

Please note that it is not necessary to determine α'' , β'' , γ'' , and δ'' since a' and b' are determined by fitting activated ^{12}C and activated ^{16}O curves to the raw decay curve of the $^{12}\text{C} + ^{16}\text{O}$ phantom (the activated $^{12}\text{C} + ^{16}\text{O}$) using the least squares method. The fractions of ^{12}C and ^{16}O can then be calculated by

$$\text{Fraction of } ^{12}\text{C} = a'/\alpha' = a \quad (8)$$

$$\text{Fraction of } ^{16}\text{O} = b'/\alpha' = b \quad (9)$$

The ^{11}C activity from the ^{12}C and ^{16}O phantoms (α and α') was determined by normalizing the PET signals from each phantom with the unit density of each atom (^{12}C or ^{16}O). The above procedure is summarized in figure 4c, which shows how the raw PET decay curve from the activated $^{12}\text{C} + ^{16}\text{O}$ phantom was decoupled into ^{12}C and ^{16}O decay curves; each curve was then decoupled into simple exponential curves that corresponded to its progeny radioisotopes. The sum of all simple exponential curves was in agreement with the raw PET decay curve. To calculate the standard error, each fitting parameter (α , β , α' , β' , γ' , α'' , and b') was calculated with not only for the best fit but also for the maximum and minimum possible values within a 95% confidence interval. This fitting parameter uncertainty in each step (^{12}C fitting, ^{16}O fitting and $^{12}\text{C} + ^{16}\text{O}$ fitting) was propagated to obtain the standard error of elemental composition estimation within the 95% confidence interval. Additionally, R^2 was calculated in each fitting to test the goodness of fit. Since short-lived isotopes such as ^{10}C decay quickly during each PET image frame acquisition time (1 min), image-frame decay correction was applied to compensate for that. To evaluate the accuracy of this technique, we compared the ^{12}C and ^{16}O fractions with the true ^{12}C and ^{16}O fractions of the $^{12}\text{C} + ^{16}\text{O}$ phantom over the depths of 0 to 10 cm.

2.3 Monte Carlo Simulation

The above analysis requires activation (PET) decay curves from the ^{12}C -only and ^{16}O -only phantoms to calculate the elemental composition from the activated $^{12}\text{C}+^{16}\text{O}$ phantom. In a clinical setting, this approach cannot be easily implemented because it is not possible to irradiate ^{12}C -only and ^{16}O -only tissue or phantom during treatment. However, we investigated whether the ^{12}C -only and ^{16}O -only phantom activation could be replaced with Monte Carlo simulation, hence restrict the activation and PET decay curve analysis to the $^{12}\text{C}+^{16}\text{O}$ phantom or patients.

A Monte Carlo simulation was performed as a step of determining the ^{12}C and ^{16}O fraction in the $^{12}\text{C}+^{16}\text{O}$ phantom. First, the near monoenergetic and SOBP proton beams that had been used in the phantom activation study were simulated using GAMOS (Geant4-based Architecture for Medicine-Oriented Simulations) (Arce *et al.* 2008). The depth-dose profiles of the simulated proton beams were in agreement within 2% and 2 mm of the actual proton beams used in this study. The Monte Carlo simulated proton energy fluence at each phantom voxel was then integrated with the proton nuclear interaction cross section data of Nishio *et al.* 2008 to simulate radioisotope creation from proton- ^{12}C and proton- ^{16}O interactions. For example, the integration of the proton energy fluence with the cross sections, $^{12}\text{C}(\text{p,pn})^{11}\text{C}$ and $^{16}\text{O}(\text{p,pn})^{11}\text{C}$ gave rise to α and α' , respectively. The MCNPX technique used by Seravalli *et al.* 2012 was followed for this Monte Carlo simulation. All cross sections used for Monte Carlo simulations were obtained from the semi-empirical equation developed by Nishio *et al.* 2005, 2008, which is in agreement with the experimental data (Iljinov *et al.* 1994) available at the EXFOR library from Brookhaven National Laboratory National Nuclear Data Center (<http://www.nndc.bnl.gov/exfor/exfor00.htm>).

α and β (the relative fractions of ^{11}C and ^{10}C in the activated ^{12}C phantom) and α' , β' , γ' (of the ^{16}O phantom) were calculated at a 1-cm depth interval using the same-sized PET VOI as those used in the PET phantom study. α , β , α' , β' , and γ' , calculated from the Monte Carlo simulation, were then used to decouple the PET signal obtained from the activated $^{12}\text{C}+^{16}\text{O}$ phantom. The same procedure used for eqs. 4–7 was used to calculate the elemental composition (fraction) of ^{12}C and ^{16}O in the $^{12}\text{C}+^{16}\text{O}$ phantom.

Once a' and b' had been determined, the elemental composition (fraction) of ^{12}C and ^{16}O in the $^{12}\text{C}+^{16}\text{O}$ phantom was calculated as follows:

$$\text{Fraction of } ^{12}\text{C} = a' / \int \int \Phi^{E_0}(\mathbf{r}, t) \sigma_{^{12}\text{C}^{11}\text{C}}(E(\mathbf{r})) d\mathbf{r} dE \quad (10)$$

$$\text{Fraction of } ^{16}\text{O} = b' / \int \int \Phi^{E_0}(\mathbf{r}, t) \sigma_{^{16}\text{O}^{11}\text{C}}(E(\mathbf{r})) d\mathbf{r} dE \quad (11)$$

Here, α and α' in eqs. 8 and 9 were replaced with the nuclear cross section, integrated over the proton energy fluence and track length. Please note that α and α' are also functions of beam irradiation time, delay, and PET acquisition time and were calculated while taking these factors into consideration. After the Monte Carlo simulation, the obtained fractions of ^{12}C and ^{16}O were compared with the true ^{12}C and ^{16}O fractions of the $^{12}\text{C}+^{16}\text{O}$ phantom over depths of 0 to 10 cm.

2.4 Clinical Study using Monte Carlo Simulations

In addition to phantom imaging, we performed 2 patient studies to validate the proposed technique and determine the ^{12}C and ^{16}O tissue composition at specific beam locations. Both patients were enrolled in the study under a MGH Investigation Review Board (IRB) approved protocol. Monte Carlo simulations were used to determine the α , β , α' , β' , and γ'

that were necessary to calculate the fractions of ^{12}C and ^{16}O in soft tissues (see details below).

Delivered doses of 2 Gy from modulated proton beams with a range of 12.5 cm and 11.7 cm were used to treat adenoid cystic carcinomas of the nasopharynx (patient 1) and lacrimal gland (patient 2), respectively; these patients underwent PET scans using a mobile PET scanner after an approximately 3-minute delay. PET data on patient 1 were acquired for 45 minutes in list mode and rebinned into 45×1 -minute frames. PET data on patient 2 were acquired for 30 minutes and rebinned into 20×1 minute frames, followed by 5×2 -minute frames. Additional information about the patient set-up and PET scans can be found in Zhu *et al* 2011.

Patient treatment beams were Monte Carlo simulated using the code developed by Paganetti *et al* (2008), which is based on GEANT4. GAMOS (Arce *et al.* 2008) was used to calculate patient dose and activation. First, patient CT DICOM files were converted into specific density and elemental compositions using the method described by Paganetti *et al* 2008, which is based on that by Schneider *et al* 2000. GEANT4-simulated patient treatment beams were irradiated on patient CT images to calculate a proton energy spectrum at each CT voxel ($0.781 \times 0.781 \times 2.5$ mm for patient 1 and $0.547 \times 0.547 \times 2.5$ mm for patient 2). By integrating the proton energy spectrum with the cross section data used above, we calculated α , β , α' , β' , and γ' (relative creation of each progeny radioisotope) for each PET voxel. Using this Monte Carlo-simulated relative creation of each radioisotope, we analyzed patient PET decay data from each voxel to calculate the relative fractions of ^{12}C and ^{16}O .

A 3-component biological diffusion model developed by Mizuno *et al* 2003, Tomitani *et al* 2003, and Parodi *et al* 2007b, 2008 was also used to account for the biological diffusion on top of the physical decay of PET signals from each voxel in patient studies. Using this biological diffusion model, we modified eq. 1 to represent the activity from the remaining radioisotopes I from the activated patient's atom T at time t after proton irradiation:

$$a_i^E(r, t) = \sum_{k=f,m,s} M_k(r) \sum_T \rho_T(r) \Phi^E(r, t) \sigma_{T1}(E(r)) (1 - e^{-(\lambda_1 + \lambda_{\text{bio},k}(r))t_R}) e^{-(\lambda_1 + \lambda_{\text{bio},k}(r))t} \quad (12)$$

where M_k ($k = f(\text{fast}), m(\text{medium}), s(\text{slow})$) is the biological decay fraction in each voxel (r) and $\lambda_{\text{bio},k}$ ($k = f(\text{fast}), m(\text{medium}), s(\text{slow})$) is the biological decay constant for the same voxel. The same biological decay parameters were multiplied in eq. 1 to account for the biologic washout of PET signals on top of physical decay. Eqs. 2 – 11 were then used to calculate the relative fraction of ^{12}C and ^{16}O in each PET voxel over the proton-irradiated tissue regions.

To reduce fluctuation of the resultant activity in each voxel ($2 \times 2 \times 1.925$ mm³), we smoothed them by averaging $3 \times 3 \times 3$ neighboring PET voxels making the volume of each voxel equal to $6 \times 6 \times 5.775$ mm³ before calculating α , β , α' , β' , and γ' and determining the relative fractions of ^{12}C and ^{16}O . To further reduce noise uncertainties, we discarded the voxels whose activity concentration was less than 8% of the maximum value in the first timeframe for patient 1 data and 20% of the maximum value for patient 2 data. These thresholds were chosen to help generate a continuous elemental tissue composition map as compared to multiple discontinuous islets. The calculated ^{12}C and ^{16}O fractions were then arranged as 2D maps and superimposed on patients' axial CT images.

Throughout this research, regression analysis was performed and R^2 (goodness of fit) was calculated between raw PET time activity curve at each PET volume / voxel. 2D map of R^2 corresponding to each PET voxel were then superimposed on the CT images.

To evaluate the accuracy of the relative fraction of ^{12}C and ^{16}O in each PET voxel of the proton irradiated tissue regions, four 2-cm² ROIs were drawn on a single plane for patient 1 (adipose 1, adipose 2, brain 1, and brain 2) and patient 2 (vitreous humor, face mask / adipose tissue, and brain), respectively. The relative fractions of ^{12}C and ^{16}O in these ROIs were then measured and compared with the published elemental composition data from ICRU 46 (ICRU Report 46).

Finally, we compared our 2D ^{16}O and ^{12}C elemental composition maps with the raw PET proton activation images to evaluate whether the latter can be a substitute for our elemental tissue composition maps. A short PET scan (0–5 minutes) raw image and delayed long PET scan raw image (15–45 minutes for patient 1 and 15–30 minutes for patient 2) were first generated and then superimposed on the axial CT slices of patients 1 and 2. A short PET scan can be considered as a pseudo-image of an ^{16}O -rich region because of the fast decay of ^{15}O . A delayed long PET scan on the other hand can be considered a pseudo-image of a ^{12}C -rich region because of the slow decay of ^{11}C . The comparison of these image pairs was done using visual assessment. The contribution from fast decaying ^{10}C was ignored due to 3 min delay from the end of activation to the beginning of PET scan.

3. Results

Figure 5 shows the depth activity profiles for three phantoms irradiated by pristine peak and SOBP beams. Each point on the graph (figure 5a, b) corresponds to the cumulated activity of the activated phantom over a period of 30 minutes. Figure 3a shows the time-activity (decay) curve of the activated ^{12}C phantom from a 4-cm³ volume ($2 \times 2 \times 1$ cm PET volume) located between the water-equivalent depths of 4 and 5 cm. The time-activity curve was decoupled into 2 simple decay curves each corresponded to a progeny radioisotope (α and β obtained in eq. 2). Figure 3b shows the time-activity curve for the activated ^{16}O phantom and the decoupled exponential curves from 3 progeny radioisotopes (α' , β' , and γ' obtained in eq. 3). Figure 4a–c shows the time-activity curve of the activated $^{12}\text{C} + ^{16}\text{O}$ phantom from the volume at the same depth (4–5 cm) and its decomposition process. First, the raw PET decay curve was separated into 4 simple exponential curves using the least-squares method (figure 4a; α'' , β'' , γ'' , and δ'' , obtained in eq. 9). This curve was decoupled into 2 decay curves—a ^{12}C decay curve and ^{16}O decay curve—by minimizing the root mean square error between the raw decay curve of the $^{12}\text{C} + ^{16}\text{O}$ phantom and the sum of the best fits of the 2 decay curves of ^{12}C and ^{16}O (figure 4b; eqs. 5–7). In this procedure, the optimal a and b (fractions of ^{12}C and ^{16}O) are obtained. The summary of the entire procedure is shown in figure 4c. Please note that in the actual calculation, α'' , β'' , γ'' , and δ'' are not computed since a and b are obtained by decoupling the raw PET decay curve into 2 decay curves—a ^{12}C decay curve and ^{16}O decay curve, however, it is shown here for illustration. Excellent goodness of fit ($R^2 > 0.994$) is shown between the raw PET decay and the sum of all decoupled radioisotope decays (fit) in both figures 3 and 4.

The procedure described above was repeated for the entire length of the phantom in 1 cm increments, and ^{12}C and ^{16}O (atomic) fractions were calculated according to eqs. 8 and 9 (eqs. 10 and 11 for the Monte Carlo method). Figure 6a, b shows the true versus estimated fractions of ^{12}C and ^{16}O in the $^{12}\text{C} + ^{16}\text{O}$ phantom for monoenergetic and SOBP proton beams, respectively. Error bars represent standard error within 95% confidence interval. Figures 7a and b show the true versus estimated fractions of ^{12}C and ^{16}O , obtained using the Monte Carlo simulation. Standard error for Monte Carlo method was smaller than that of PET measurement method since the latter method involved 3 steps of fitting which propagated to a larger error while the former method required only one fitting ($^{12}\text{C} + ^{16}\text{O}$). Both elemental decomposition methods (the PET measurement and Monte Carlo methods) estimated the fraction of ^{12}C and ^{16}O within a 3.6% difference, with the true fraction for

both beams over the depths of 0–8 cm. Regression analysis was performed on all intermediate (^{12}C and ^{16}O phantoms) and final ($^{12}\text{C} + ^{16}\text{O}$ phantom) processes and their goodness of fit (R^2) were equal to or greater than 0.992 in all 10 PET volumes (figures 6, 7).

Table 3 shows the elemental composition of ^{12}C and ^{16}O in 4 ROIs drawn in patient 1 (figure 8a) and a comparison with the ICRU 46 data. Standard deviation of measurement in each ROI is the same for both ^{12}C and ^{16}O since ^{12}C fraction is a complement of ^{16}O fraction. Table 4 reveals the same results for the 4 ROIs drawn in patient 2 (figure 9a) and the ICRU 46 data. For patient 1, short and delayed long PET scans were overlaid on the CT image (figures 8a, b). The calculated relative fractions of ^{16}O and ^{12}C for the same axial slice are shown in figures 8c, d. The 2D map representing the goodness of fit (R^2) between each PET voxel time activity curve and its corresponding fitted activity curve is shown in figure 8e. Over 95% of the PET voxel shows R^2 greater than 0.7 which represent good fits. A raw PET decay curve of a PET voxel and its fitting are shown as an example in figure 8f. Similar results for patient 2 are shown in figures 9a–f.

4. Discussion

In order to improve the accuracy of dose calculations in proton therapy, an accurate tissue element composition is required to improve the calculation of tissue stopping powers. However, no imaging techniques can be used to determine tissue elemental composition. Moreover, the composition can vary significantly between individuals (ICRU Report 46); hence, the average elemental composition of each organ should not be generalized across the patient population. In this regard, the best solution for optimal proton treatment planning is to determine individual patient elemental tissue composition in the same way that individual electron density information is provided by CT.

In this study, we developed a technique that decouples positron emission decays after proton activation into their constituent elemental composition. The proposed elemental decomposition method estimated the fraction of ^{12}C and ^{16}O , with good accuracy, over a depth of 0–8 cm (figure 6). The accuracy at 8–10 cm, however, was lower. This lower accuracy can be attributed to: a) the small number of positrons generated at this depth, b) the rapid changes of α , β , α' , β' , and γ' near the distal penumbra of the proton beams and c) the differences in water equivalent thickness scaling between different phantoms. The peak of the nuclear interaction cross section occurs at around 40–50 MeV, below this energy, the activation of ^{12}C and ^{16}O decreases rapidly and α , β , α' , β' , and γ' also changes rapidly due to the cross section changes (figure 2). Proton energies at depths of 8–10 cm are mostly at the lower energy spectrum; therefore, the smaller number of positrons generated results in increased statistical uncertainty. When summed with other uncertainties mentioned above, these lead to a larger discrepancy between the measured and true fractions.

Schneider *et al* 2000 correlated CT numbers with elemental tissue composition, such as hydrogen, nitrogen, phosphorus, and calcium, within a few percentage points. Their correlation for oxygen and carbon, however, was uncertain to 23%. In other words, using CT numbers alone, it was difficult to estimate the elemental composition of oxygen and carbon better than 23%. This work complements the work of Schneider *et al* 2000 in that it can provide tissue elemental composition, which cannot be determined using CT data alone.

The Monte Carlo simulation estimated the fraction of ^{12}C and ^{16}O with similar differences to the truth compared with the PET measurement method. The PET measurement method, however, requires the activation of pure ^{12}C and ^{16}O phantoms to determine α , β , α' , β' , γ' and hence calculate the ^{12}C and ^{16}O elemental fraction in the $^{12}\text{C} + ^{16}\text{O}$ phantom. The Monte Carlo method on the other hand does not require this information since the

corresponding α , β , α' , β' , γ' can be obtained directly from Monte Carlo simulation. The Monte Carlo method was developed particularly for patient tissue element decomposition because only 1 measurement (patient proton activation and PET scan) is feasible in patient studies. However, it is worth mentioning that irradiation of the ^{12}C -only and ^{16}O -only phantoms using the same patient beam might be possible to obtain α , β , α' , β' , and γ' in order to conduct the patient elemental composition analysis. However, this method requires scaling for density differences between phantoms and patients which can be quite complicated.

The ^{12}C and ^{16}O fractions calculated from the 7 ROIs in the patient studies showed good agreement with the ICRU data (tables 3 and 4). For patient 2 (figure 9), the ^{16}O fraction map constructed using the least-squares method was similar to the short PET scan. In addition, the ^{12}C map for this patient was also quite similar to the delayed long PET scan. In this regard, one could suggest that short and delayed long PET scans can be used to show the fractional distribution of ^{16}O and ^{12}C . However, such a suggestion is flawed because a ^{16}O -rich tissue region that is strongly activated by protons will have strong ^{15}O signals while another ^{16}O -rich tissue region that is weakly activated by protons will have weak ^{15}O signals and hence would not reflect its corresponding ^{16}O -rich content. Therefore, short or delayed long PET scans which depend on the magnitude of activation cannot be used to determine the ^{16}O and ^{12}C elemental fractions. Our proposed method of elemental decomposition, on the other hand, can provide ^{16}O and ^{12}C fraction information, regardless of the regional activation magnitude, because the maps are constructed from decay schemes rather than from absolute PET signal magnitudes. As an example, for patient 1 (figure 8), the difference between the short and delayed long scans is not clear because they are strongly dependent on the absolute magnitude of the activation.

The results of the goodness of fit (R^2) of the patient studies are worse than those for the phantom study. This is not surprising considering the volume of PET voxels for patient studies were 20 times smaller than for the phantom study. The difference in voxel volume is also reflected in the smoothness of the raw PET decay curves of the phantom study (figure 4) as compared to the large fluctuation (figures 8f and 9f) seen in the patient studies. Although the model equation as well as its fitting is satisfactory, the large variance from this fluctuation resulted in lower R^2 values in patient studies compared to the phantom studies. PET signal averaging with adjacent voxels reduced this fluctuation and on average provided better goodness of fit over the large patient volume. The goodness of fit for patient 1 was worse than that of patient 2. This is partly due to a lower PET signal threshold for patient 1 (8% of maximum) than patient 2 (20% of maximum). When the PET signal threshold was increased, the goodness of fit improved (data not shown).

To our knowledge, this is the first investigation of the use of PET imaging to determine elemental tissue composition after proton therapy. This method was demonstrated for 2 elements (^{12}C and ^{16}O) in a soft tissue region and hence represents a feasibility study. Attempts to analyze ^{12}C and ^{16}O fractions in non-soft tissue regions (for example, bone) may lead to large errors if ^{31}P and ^{40}Ca activation is not included, as both exist in large quantities in bone. The proposed method can be extended to include more elements, such as ^{14}N , ^{31}P , and ^{40}Ca , although the accuracy of the least-squares method is expected to decrease with increasing numbers of tissue elements. In this research, evaluating ^{12}C and ^{16}O only is justified in soft tissue because the fraction of other proton-activated elements (N, Na, P, S, Cl, and K) is quite small (3%–4%) (ICRU 46, Woodard and White 1986).

One limitation of the proposed approach is that it depends on an in-room or on-site PET scanner because of the fast-decaying but essential radioisotope, ^{15}O . The need for a PET

scanner can be cost prohibitive for many proton therapy centers. Another limitation of the proposed approach is the lack of an isotope-specific biological diffusion model. Each radioisotope will likely have a different biological diffusion. For example, ^{15}O is expected to wash out faster than ^{11}C because oxygen is a main element of water whereas carbon is the main element of adipose tissue and cell membranes. However, because no isotope-specific diffusion models exist, a non-isotope specific biological diffusion model was used in this study. An isotope-specific model is expected to improve the accuracy of tissue elemental composition estimation. A third limitation of this approach is its dependence on the accuracy of the least squares method in separating the raw PET decay curve into its constituent tissue elements. The robustness of the proposed approach against fluctuations in PET raw decay curves is the focus of another study currently under investigation. Additionally, it should be stated that the accuracy of the proposed method is subject to the uncertainty of the cross section data. More accurate and universally accepted cross section measurement and data are required for more accurate elemental composition calculation. In this work all cross sections data used for the Monte Carlo simulations were obtained from Nishio *et al* 2005, 2008, which is in agreement with the experimental data (Iljinov *et al* 1994) available at the EXFOR library from Brookhaven National Laboratory National Nuclear Data Center (<http://www.nndc.bnl.gov/exfor/exfor00.htm>).

In practice, we envision each patient receiving the planned proton treatment which is planned using a conventional approach with relative stopping powers deduced from tissue's Hounsfield unit information alone. Immediately after the first treatment, the patient receives a PET scan which provides the patient elemental tissue composition information using the above technique. The obtained elemental tissue composition information can then be used to refine the treatment plan and improve treatment verification using PET. The elemental composition of tissues may change over the course of treatment due to, for example, the change of oxygenation and radiation induced necrosis. Future studies will address these problems as well as sensitivity of the proposed method on different tissues and biological washout.

5. Conclusions

The proposed technique—elemental tissue decomposition using PET after proton activation—determined the elemental fractions of ^{12}C and ^{16}O with an uncertainty of 7.2% in the phantom studies. The technique was used to estimate the tissue ^{12}C and ^{16}O elemental composition in the soft tissue region in the head of 2 patients who underwent proton therapy. The estimated ^{12}C and ^{16}O elemental composition of 7 ROIs was in agreement with the ICRU 46 elemental composition data with an uncertainty of 15.2%. The proposed techniques can be used to estimate ^{12}C and ^{16}O elemental composition in soft tissue, which can be used to improve treatment planning and proton treatment verification using PET.

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Figure 1.

A 12-cm long phantom was irradiated with near monoenergetic and 6-cm SOBP proton beams, followed by PET scans. It consisted of three sections composed of high-density polyethylene (HDPE), water gel, and tissue gel, respectively.

Figure 2.
Proton nuclear interaction cross sections of ^{12}C and ^{16}O (Nishio *et al* 2008).

(a)

(b)

Figure 3.

(a) Activated ^{12}C was decoupled into 2 simple exponential decay curves that corresponded to progeny radioisotopes, ^{11}C and ^{10}C . The sum of those 2 exponential decay curves was in agreement with the original PET decay curve. (b) Activated ^{16}O was decoupled into 2 simple exponential decay curves that corresponded to progeny radioisotopes: ^{11}C , ^{13}N , and ^{15}O . The sum of those 3 exponential decay curves was in agreement with the original PET decay curve. The raw PET decay curve from the activated $^{12}\text{C}+^{16}\text{O}$ was decoupled into the ^{12}C and ^{16}O decay curves, and their sum was in agreement with the raw PET decay curve. Goodness of fit (R^2) is shown.

(a)

(b)

(c)

Figure 4.

(a) Activated $^{12}\text{C}+^{16}\text{O}$ were decoupled into 4 simple exponential decay curves that corresponded to the progeny radioisotopes ^{10}C , ^{11}C , ^{13}N , and ^{15}O . The sum was in close agreement with the raw PET decay curve. (b) The curve from the activated $^{12}\text{C}+^{16}\text{O}$ was decoupled into the ^{12}C and ^{16}O decay curves, and their sum was in agreement with the raw PET decay curve. (c) The original decay curve of activated $^{12}\text{C}+^{16}\text{O}$ was decoupled into ^{12}C and ^{16}O decay curves; each of these was decoupled into their progeny simple exponential decay curves.

Here, the magnitude of ^{12}C and ^{16}O (a, b in eq. 5) was proportional to the fraction of ^{12}C and ^{16}O in the $^{12}\text{C}+^{16}\text{O}$ phantom. Goodness of fit (R^2) is shown.

(a)

(b)

Figure 5.

(a) Depth activation curves of 3 phantoms irradiated by a monoenergetic proton beam. (b) Depth activation curves of 3 phantoms irradiated with an SOBP beam.

(a)

(b)

Figure 6. PET measurement method. (a) Estimated ^{12}C and ^{16}O (atomic) fractions at each phantom depth for a near monoenergetic beam. True fractions are shown as straight lines (refer to table 1). (b) Estimated ^{12}C and ^{16}O (atomic) fractions at each phantom depth for a SOBP beam. True (atomic) fractions are shown as straight lines. Error bars represent standard error at 95% confidence interval.

(a)

(b)

Figure 7.

Monte Carlo method. (a) Estimated ^{12}C and ^{16}O (atomic) fractions at each phantom depth for a near monoenergetic beam. True fractions are shown as straight lines (refer to table 1). (b) Estimated ^{12}C and ^{16}O (atomic) fractions at each phantom depth for a SOBP beam. True (atomic) fractions are shown as straight lines. Error bars represent standard error at 95% confidence interval.

Figure 8.

Patient 1: (a) Short PET scan (0–5 minutes) overlaid on top of axial CT image, 4 ROIs are drawn. (b) Delayed long PET scan (15–45 minutes), proton beam direction is shown. (c) ^{16}O relative fraction map. (d) ^{12}C relative fraction map. (e) 2D map of goodness of fit (R^2). (f) PET decay curve of a PET voxel and its fitting using the least squares method.

Figure 9.

Patient 2: (a) Short PET scan (0–5 minutes) overlaid on top of axial CT image, 4 ROIs are drawn. (b) Delayed long PET scan (15–30 minutes), proton beam direction is shown. (c) ^{16}O relative fraction map. (d) ^{12}C relative fraction map. (e) 2D map of goodness of fit (R^2). (f) PET decay curve of a PET voxel and its fitting using the least squares method.

Table 1

Elemental compositions of three phantoms.

Phantom	Elemental composition (% by weight)			
	¹⁶ O	¹² C	¹ H	¹⁴ N
HDPE (¹² C phantom)	0.0	85.7	14.3	0.0
Water gel (¹⁶ O phantom)	87.6	1.04	11.03	0.32
Tissue gel (¹² C+ ¹⁶ O phantom)	73.8	14.9	9.6	1.46
Elemental composition (% by atomic fraction)				
Tissue gel (¹² C+ ¹⁶ O phantom)	78.8	21.2	Fractions of ¹ H and ¹⁴ N not counted	

Natural abundances of the above isotopes are 98.89%–99.99%.

¹H is not proton activated and therefore does not contribute to positron emission.

Table 2

Proton interaction channels and half-lives of β^+ emitting progeny radioisotopes of ^{12}C and ^{16}O .

Element	Proton-element interaction channel (half-life of progeny radioisotope)
^{12}C	$^{12}\text{C}(\text{p,pn})^{11}\text{C}$ (20.23 min), $^{12}\text{C}(\text{p,p2n})^{10}\text{C}$ (19.29 sec)
^{16}O	$^{16}\text{O}(\text{p},\alpha\text{pn})^{11}\text{C}$ (20.23 min), $^{16}\text{O}(\text{p},\alpha)^{13}\text{N}$ (9.96 min), $^{16}\text{O}(\text{p,pn})^{15}\text{O}$ (122.24 sec)

$^{16}\text{O}(\text{p,p2n})^{14}\text{O}$ (70.61 sec) and $^{16}\text{O}(\text{p,3p4n})^{10}\text{C}$ were ignored because of their small contributions (small interaction cross sections and short half-lives).

Table 3

Patient 1: Calculated elemental compositions vs. ICRU 46 data for 4 ROIs.

ROI	Elemental composition (% by atomic fraction)						
	Calculation			ICRU 46			Difference
	Average		Standard deviation (%)	Standard deviation (%)		Difference	Difference
	¹⁶ O	¹² C		¹⁶ O	¹² C		
Adipose tissue 1	36.7	63.3	6.1	34.0	66.0	2.7	
Adipose tissue 2	21.4	78.6	4.0	34.0	66.0	12.6	
Brain 1	61.7	27.8	7.7	78.6	21.4	6.4	
Brain 2	65.9	34.1	12.1	78.6	21.4	12.7	

* The difference was calculated by subtracting true percentage fractions with estimated fractions.

Table 4

Patient 2: Calculated elemental compositions vs. ICRU 46 data for 4 ROIs.

Elemental composition (% by atomic fraction)							
ROI	Calculation		ICRU 46		Difference		
	Average		Standard deviation (%)				
	¹⁶ O	¹² C	¹⁶ O	¹² C	¹⁶ O	¹² C	(%)
Vitreous humor	95.5	4.5	4.5	98.5	1.5	3.0	
Adipose tissue/ face mask	7.7	92.3	10.8	-	-	-	
Adipose tissue only	20.9	79.1	10.2	34.0	66.0	13.1	
Brain	63.4	36.6	8.5	78.6	21.4	15.2	

* The difference was calculated by subtracting true percentage fractions with estimated fractions.