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2006 Phys. Med. Biol. 51 5769

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Development of dose delivery verification by PET imaging of photonuclear reactions following high energy photon therapy

S Janek¹, R Svensson¹, C Jonsson^{1,2} and A Brahme¹

¹ Medical Radiation Physics, Department of Oncology and Pathology, Karolinska Institutet and Stockholm University, Box 260, 171 76 Stockholm, Sweden

² Department of Medical Physics/Nuclear Medicine, Karolinska University Hospital, 171 76 Stockholm, Sweden

E-mail: sara.janek@ki.se

Received 11 April 2006, in final form 12 September 2006

Published 19 October 2006

Online at stacks.iop.org/PMB/51/5769

Abstract

A method for dose delivery monitoring after high energy photon therapy has been investigated based on positron emission tomography (PET). The technique is based on the activation of body tissues by high energy bremsstrahlung beams, preferably with energies well above 20 MeV, resulting primarily in ¹¹C and ¹⁵O but also ¹³N, all positron-emitting radionuclides produced by photoneutron reactions in the nuclei of ¹²C, ¹⁶O and ¹⁴N. A PMMA phantom and animal tissue, a frozen hind leg of a pig, were irradiated to 10 Gy and the induced positron activity distributions were measured off-line in a PET camera a couple of minutes after irradiation. The accelerator used was a Racetrack Microtron at the Karolinska University Hospital using 50 MV scanned photon beams. From photonuclear cross-section data integrated over the 50 MV photon fluence spectrum the predicted PET signal was calculated and compared with experimental measurements. Since measured PET images change with time post irradiation, as a result of the different decay times of the radionuclides, the signals from activated ¹²C, ¹⁶O and ¹⁴N within the irradiated volume could be separated from each other. Most information is obtained from the carbon and oxygen radionuclides which are the most abundant elements in soft tissue. The predicted and measured overall positron activities are almost equal (−3%) while the predicted activity originating from nitrogen is overestimated by almost a factor of two, possibly due to experimental noise. Based on the results obtained in this first feasibility study the great value of a combined radiotherapy–PET–CT unit is indicated in order to fully exploit the high activity signal from oxygen immediately after treatment and to avoid patient repositioning. With an RT–PET–CT unit a high signal could be collected even at a dose level of 2 Gy and the acquisition time for the PET could be reduced considerably. Real patient dose delivery verification by means of PET imaging seems to

be applicable provided that biological transport processes such as capillary blood flow containing mobile ^{15}O and ^{11}C in the activated tissue volume can be accounted for.

1. Introduction

Positron emitters used for PET imaging have relatively short half-lives, about 20 min for ^{11}C , 10 min for ^{13}N and 2 min for ^{15}O . Since ^{11}C , ^{13}N and ^{15}O are all bio-isotopes and the building blocks of all living organisms they can be labelled in almost any organic molecule to very closely follow the dynamics of biochemical processes in tumours and healthy tissues. During high energy external photon beam therapy, ^{11}C , ^{13}N and ^{15}O are also the main PET emitters produced by photonuclear reactions in tissue. They are primarily produced by (γ, n) reactions and the threshold energy is in the range 11–18 MeV as seen in figure 1. To maintain a high quality in radiation therapy it is necessary to have a precise system for dosimetric verification. This is particularly important when intensity-modulated radiation therapy (IMRT) is used and small misalignments can cause severe normal tissue side effects and underdosage in the target. Deviations in the delivered dose from that in the treatment plan may occur because of errors in the dose delivery, treatment planning, patient positioning, bowel gas and organ motion or other local changes of the anatomy of the patient over a fractionated treatment series. By combining high energy external beam photon treatment with PET imaging the activated tissue in a patient can be measured and it may be possible to investigate and control dose delivery compared to that in the treatment plan (Janek 2003, Brahme 2003).

^{15}O activity studies of tumour blood flow trying to quantify tumour vasculature were pioneered by Hughes *et al* (1979) and Ten Haken *et al* (1981) using a 45 MV betatron beam and by Nussbaum *et al* (1983) using a 30 MV beam from a Clinac-35 linear accelerator. Apart from these very early studies, the possibility of proton therapy monitoring by means of PET was recently investigated (Parodi and Enghardt 2000, Parodi *et al* 2001). Integration of a PET scanner with light ion therapy was done in the treatment facility at Gesellschaft für Schwerionenforschung (GSI), Darmstadt, Germany (Enghardt *et al* 1992, 2004, Pawelke *et al* 1996, Pönisch *et al* 2004) as well as at the Heavy Ion Medical Accelerator at Chiba (HIMAC), Japan (Iseki *et al* 2004). The possible application of PET imaging during photon therapy was investigated by Muller and Enghardt (2006) using Geant4.

The aim of this paper is to investigate PET imaging of photonuclear reactions following high energy photon therapy as a method to quantify and verify the delivered dose distribution. Therapy verification could be achieved by comparing the measured positron activity distribution with the expected one calculated during treatment planning. The calculation must be based on the anatomical information of the patient as well as the time course of the delivered beams. The mean dose distribution delivered to the patient averaged over the whole treatment fraction could then be verified by PET imaging and used during the following treatments to correct for possible errors during the previous dose delivery. Organ motions in the PET camera can be reduced by using respiratory and cardiac triggering. The accelerator used in the present study is a Racetrack Microtron at Karolinska University Hospital utilizing 50 MV scanned photon beams (Brahme 1987, Svensson *et al* 1998). Studies have been made on a homogeneous PMMA phantom and a piece of frozen tissue, the hind leg of a pig. The latter contains all the important elements that are interesting to study but avoids the complication of vascular dynamics present in living tissues.

Figure 1. Comparison of the photoneutron cross sections (γ, n) for ^{12}C , ^{14}N , ^{16}O , ^{31}P and ^{40}Ca (Experimental Nuclear Reaction Data, EXFOR/CSISRS) with the Monte Carlo calculated 50 MV scanned photon beam fluence spectra differential in energy Φ_E from a 5W7.25Cu bremsstrahlung target (Holmberg 2006) at the central axis Φ_{axis} and near the field border $\Phi_{\text{off-axis}}$. Due to the lack of experimental data at high energies the neutron production cross sections for ^{12}C and ^{16}O are based on (γ, n_0) data from the IAEA Photonuclear Data Library (Chadwick and Young 1999) for energies above 26.4 MeV and 23 MeV, respectively.

2. Methods and materials

2.1. Photonuclear reactions

In the patient, photonuclear reactions may be induced by energetic photons that excite the nuclei which then may emit nuclear particles such as neutrons, protons, alphas and ^3He depending on the nuclei of the irradiated tissue and the photon energy spectrum. The emission process is generally governed by the vibrational state of the protons and neutrons induced by the photon excitation. Most important in this respect is the collective giant dipole resonance, and the energy and angular distributions of the emerging photonuclear fragments therefore depend strongly on the photon energy and the target nuclei (Hayward 1970). For photon energies above 30 MeV, the dominant processes are photoneutron and photoproton production where the (γ, n) and (γ, p) cross sections are rather similar in magnitude and shape (Fuller 1985). The photoneutron reaction is of main interest in this study since photoproton reactions do not generally generate positron-emitting radionuclides and hence do not contribute to the PET activity. The elemental composition of common body tissues is presented in table 1 based upon ICRU Report 46 (ICRU 1992). The main photoneutron reactions resulting in the production of the positron-emitting radionuclides are $^{12}\text{C}(\gamma, n)^{11}\text{C}$, $^{14}\text{N}(\gamma, n)^{13}\text{N}$, $^{16}\text{O}(\gamma, n)^{15}\text{O}$, $^{31}\text{P}(\gamma, n)^{30}\text{P}$ and $^{40}\text{Ca}(\gamma, n)^{39}\text{Ca}$ with 20.4 min, 9.97 min, 2.04 min, 2.50 min and 0.86 s half-lives, respectively. The distance that the energetic positrons travel before annihilation is determined by the surrounding tissue and the maximum positron energy which for ^{11}C , ^{13}N and ^{15}O are 0.96, 1.20 and 1.73 MeV, respectively (Ekström and Firestone 1999). The more rare element ^{31}P , listed in table 1, as well as the unlisted elements ^{18}O , ^{13}C , ^{15}N , ^{23}Na , ^{nat}Cl (^{35}Cl (75.5%), ^{37}Cl (24.5%)), ^{32}S and ^{39}K (contents less than 0.9%), are responsible for less than 2% of the produced neutrons and protons (Gudowska *et al* 1999). Positron emitters

Table 1. Elemental composition for some well-known body tissues (adult male, ICRU 1992) together with water, carbon, nitrogen and oxygen. Tissues with element contents less than 0.4% are not tabulated. ρ , $\int \sigma_{\gamma,n}(E) dE$ and $\rho \cdot \int \sigma_{\gamma,n}(E) dE$ are the density, the integrated cross section and the integrated cross section weighted with density. Integration is performed from photoneutron threshold energy to 50 MeV.

Tissue/material	Elemental composition (percentage by mass)					ρ (g cm ⁻³)	$\int \sigma_{\gamma,n}(E) dE$ (MeV cm ² g ⁻¹)	$\rho \int \sigma_{\gamma,n}(E) dE$ (MeV cm ⁻¹)
	¹ H	¹² C	¹⁴ N	¹⁶ O	Others			
Adipose tissue	11.4	59.8	0.7	27.8	<0.4	0.95	2.22	2.11
Average soft tissue	10.5	25.6	2.7	60.2	<0.4	1.03	1.72	1.77
Blood	10.2	11	3.3	74.5	<0.4	1.06	1.57	1.66
Lipid	11.8	77.3	–	10.9	–	0.92	2.27	2.08
Muscle (skeletal)	10.2	14.3	3.4	71	<0.4	1.05	1.60	1.68
Skeleton-cortical bone	3.4	15.5	4.2	43.5	10.3 ³¹ P, 22.5 ⁴⁰ Ca	1.92	1.21	2.32
Skeleton-femur	7	34.5	2.8	36.8	5.5 ³¹ P, 12.9 ⁴⁰ Ca	1.33	1.59	2.11
Skeleton-spongiosa	8.5	40.4	2.8	36.7	3.4 ³¹ P, 7.4 ⁴⁰ Ca	1.18	1.74	2.06
Red marrow	10.5	41.4	3.4	43.9	<0.4	1.03	1.90	1.96
Yellow marrow	11.5	64.4	0.7	23.1	<0.4	0.98	2.13	2.09
Water	11.2	–	–	88.8	–	1.00	1.43	1.43
Carbon (solid)	–	100	–	–	–	1.80–3.52	2.70	4.86–9.50
Nitrogen (gaseous)	–	–	100	–	–	1.25×10^{-3}	2.22	2.77×10^{-3}
Oxygen (gaseous)	–	–	–	100	–	143×10^{-3}	1.61	2.29×10^{-3}

can also be produced through reactions such as $^{16}\text{O}(\gamma, 2n)^{14}\text{O}$, $^{16}\text{O}(\gamma, t)^{13}\text{N}$, $^{16}\text{O}(\gamma, \alpha n)^{11}\text{C}$ and $^{12}\text{C}(\gamma, 2n)^{10}\text{C}$. However, the integrated photonuclear cross sections for these reactions constitute, respectively, 0.5%, 0.8%, 3.5% and 0.2% of the respective integrated photoneutron cross section (Fuller 1985). As shown in figure 1, the peaks of the photoneutron cross sections, $\sigma_{\gamma,n}(E)$, are often in the photon energy range 18–25 MeV. The weighted photoneutron cross sections for different tissues in cm² g⁻¹ are shown in figure 2 and listed in table 1. The production of radionuclides per unit volume will depend on both the photoneutron cross section and the physical density ρ . Although the cross sections for ^{31}P and ^{40}Ca are quite large, their contributions to tissue activation are only a few per cent due to the rare occurrence of these elements in most tissues except for bony structures. Presently, the focus is on the dominant (γ, n) reactions and the most abundant elements present in the body tissue such as oxygen, carbon and nitrogen, since calcium has too short a half-life to be detected after the patient has been brought outside the treatment room.

2.2. Activation of tissue

The activation of tissue by high energy photons can be described by a linear first-order differential equation. For the radionuclide χ let ${}^{\chi}\sigma_{\gamma,n}(E)$ be the photoneutron cross section and ${}^{\chi}N_{\text{T}} = \rho N_{\text{A}} w / M$ the number of target atoms per cm³, where N_{A} is Avogadro's constant, w is the mass fraction from table 1 and M is the molar mass. Then the rate of production of radioactive atoms per unit volume (in unit time) will be equal to ${}^{\chi}N_{\text{T}} \int_E \varphi_E(t, E) {}^{\chi}\sigma_{\gamma,n}(E) dE$, where $\varphi_E(t, E)$ is the photon fluence rate differential in energy. Once these radionuclides have been produced, their number reduces with time at a rate ${}^{\chi}\lambda {}^{\chi}N(t)$ due to the physical process of

Figure 2. Overlay of the (γ, n) cross section and the mass energy absorption coefficient for cortical bone, average soft tissue and adipose tissue (ICRU 1992) together with the photon energy fluence spectra Ψ_E differential in energy (Holmberg 2006).

decay. Because activity is also lost from the body as a result of biological transport processes, including capillary blood flow containing mobile ^{15}O but also mobile ^{11}C in the activated tissue volume, there will be a second reduction term $G(t)$ when the activation process involves living tissue. Thus, the net rate at which the population of active atoms per cm^3 accumulate can be expressed as

$$\frac{d^{\chi}N(t)}{dt} = {}^{\chi}N_T \int_{E_t}^{E_m} \varphi_E(t, E) {}^{\chi}\sigma_{\gamma,n}(E) dE - {}^{\chi}\lambda {}^{\chi}N(t) - G(t) \quad (1)$$

where the integration is from the threshold energy E_t for the photonuclear cross section to maximum photon energy of the bremsstrahlung spectrum E_m . Two assumptions are now made: (i) in this paper, where the study is focused on frozen material, the biological rate constants are zero and we further assume that $G(t) = 0$. (ii) The Racetrack Microtron operates at a pulse repetition frequency of 200 Hz, thus completing almost two full scans per second. For simplicity we assume that the mean photon fluence rate is constant with time and equal to $\varphi_E(E)$ since the pulse structure is unimportant as the scan pattern repetition rate of 0.5 s per scan is much smaller than the mean life ${}^{\chi}\lambda^{-1}$ of the radionuclide of interest. Now, through the integration of equation (1), assuming the initial activity to be zero (${}^{\chi}A = {}^{\chi}\lambda {}^{\chi}N = 0$ at $t = 0$), the number of disintegrations of radionuclide χ in Bq cm^{-3} before and after the end of irradiation t_{irr} will be given by

$${}^{\chi}A(t) = \begin{cases} {}^{\chi}N_T \int_E \varphi_E(E) {}^{\chi}\sigma(E) dE [1 - \exp(-{}^{\chi}\lambda t)] & t \leq t_{\text{irr}} \\ {}^{\chi}N_T \int_E \varphi_E(E) {}^{\chi}\sigma(E) dE [1 - \exp(-{}^{\chi}\lambda t_{\text{irr}})] \exp(-{}^{\chi}\lambda t) & t > t_{\text{irr}}. \end{cases} \quad (2)$$

Since the PET camera has an efficiency less than one, the observed specific count rate ($\text{s}^{-1} \text{cm}^{-3}$) is always less than the disintegration rate and may for radionuclide χ with activity

${}^XA(t, \mathbf{r}')$ at a point $\mathbf{r}'$ and a specific tissue be written as

$${}^XS(t, \mathbf{r}) = \varepsilon(\mathbf{r}) \int \int_{V'} \int {}^XA(t, \mathbf{r}') {}^XP(\mathbf{r}, \mathbf{r}') d^3\mathbf{r}' \quad (3)$$

where $\varepsilon(\mathbf{r})$ is the counting efficiency correcting for attenuation of the radiation in escaping the object, geometrical factors and other effects. ${}^XP(\mathbf{r}, \mathbf{r}')$ is a point spread function that determines the spatial resolution loss due to several physical properties of the camera and the imaged object. The most important are positron range, detector size, non-collinearity of annihilation photons and varying depth of interaction of photons in the detectors. Positron range depends only on the radionuclide and the material traversed whereas detector size, non-collinearity and depth of interaction depend solely on the position of the annihilation event, geometry and physical properties of the detector system (Levin and Hoffman 1999, Sanchez-Crespo *et al* 2004, Sanchez-Crespo and Larsson 2006). The overall system spatial resolution is a mathematical convolution of all distributions. Much effort by other authors is devoted on modelling and calculating these complexities and will not be analysed further in this paper. Nevertheless, the errors associated with these effects are important to consider when studying the acquired PET images.

2.3. Instrumentation

2.3.1. PMMA phantom. A solid polymethyl methacrylate phantom (PMMA, composition: $C_5H_8O_2$; density: 1.17 g cm^{-3}) with dimensions $30 \times 30 \times 10 \text{ cm}^3$ (see figure 3) was used to investigate the beam dose and activity profile in a uniform medium.

2.3.2. Pig leg. To investigate the quality and sensitivity of the PET technique, a frozen hind leg of a pig (see figure 4(a)) was used.

2.3.3. PET cameras. PET scans of the PMMA phantom were performed with an ECAT EXACT 921 scanner (SIEMENS/CTI, Knoxville, TN, USA) operating in 2D. PET scans of the pig leg were performed with an ECAT EXACT HR scanner (SIEMENS/CTI, Knoxville, TN, USA) operating in 3D. The transaxial FWHM at 0 cm without smoothing filter is 5 mm (HR, Jonsson *et al* 1998) and 6 mm (921, Siemens data sheet). Emission data were reconstructed by an iterative reconstruction algorithm using two iterations and eight subsets. Transmission scans for attenuation correction were performed with ${}^{68}\text{Ge}$ rod sources and reconstructed by filtered backprojection. All data were corrected for random coincidences, dead time, scatter and attenuation. A 6 mm Gaussian filter was applied in the 2D reconstruction (921) and a 2 mm Gaussian filter in the 3D reconstruction (HR).

2.3.4. CT and treatment planning. The 3D radiation treatment planning system, Helax-TMS, was used to calculate the delivered dose distributions. The PMMA phantom was directly simulated in the Helax-TMS without prior CT scan. 3D radiation treatment planning on the pig leg was preceded by a CT scan on a Siemens Somatom (Siemens, Erlangen, Germany).

2.3.5. Radiotherapy. Irradiations were performed with scanned photon beams produced by a 50 MeV electron beam from the Racetrack Microtron (Scanditronix, IBA, Uppsala, Sweden) installed at the Karolinska University Hospital. The dose rate during irradiation was about 2 Gy min^{-1} . The photon fluence differential in energy Φ_E of the scanned 50 MV beam from the Racetrack Microtron is shown in figure 1 and the photon energy fluence differential in energy Ψ_E in figure 2. The data were obtained by Monte Carlo calculations using Geant4

Figure 3. Activation image of the 50 MV scanned photon beam irradiation of the PMMA phantom with a square field of $30 \times 30 \text{ cm}^2$ at the phantom surface, totally given 10 Gy. Isodoses are in the range 40–100% of total dose in steps of 10%. The cross-beam activity, $S(x)/\hat{S}$, and dose distributions, $D(x)/\hat{D}$, are shown for depths $z = 2.6$ and 10.2 cm where the dose is normalized to depth dose max D and the activity to its own integrated area $\hat{S}$.

(Holmberg 2006) where the photon beam is produced by scanned 50 MeV electrons incident on a 5 mm Tungsten + 7.25 mm Copper (5W7.25Cu) bremsstrahlung target, producing almost uniform photon beam dose distributions. The scanned uniform photon beam is produced by a first circular scanning pattern with 115 elementary pencil beam shots at 14.5 cm radius and a second one with 6 elementary pencil beam shots at 5.0 cm radius. The source to isocentre distance was 100 cm and a uniform dose over a $30 \times 30 \text{ cm}^2$ field is obtained. The spectra displayed in figure 1 represents the photon fluence differential in energy on the central axis (dotted) and 11.6 cm from the central axis (solid) at 0.4 cm depth below the phantom surface, both averaged over an area of $2 \times 2 \text{ cm}^2$.

2.4. Phantom studies

The contour of the PMMA phantom with an overlaid projection of the 3D treatment plan is shown in figure 3 for a central transaxial plane. In figure 4(b), the radiation treatment plan for the pig leg is shown. A four-field box technique consisting of four scanned photon beams was used. The calculated isodose levels are shown as dashed lines in the range 10–90% of total dose 10 Gy in steps of 10%. The radiation field at the PMMA phantom surface was $30 \times 30 \text{ cm}^2$ and on the pig leg $10 \times 10 \text{ cm}^2$ at isocentre. Irradiation time of the single scanned beam on the PMMA phantom was 313 s and the delivery of four scanned beams on the pig leg was completed in a time of 300 s including the extra time needed for gantry rotation. The

Figure 4. Totally 10 Gy, for each field a dose of 2.5 Gy, was given using a 50 MV scanned photon beam. (a) Tissue variations within the optical image cut out after treatment. (b) The pig leg was irradiated with a four-field box technique ($10 \times 10 \text{ cm}^2$), marked as numbers from 1 to 4, where 1 denotes the first beam executed and 4 the last. (c) Overlay of PET image plane 12 for frame 1 and CT. (d) Overlay of PET image with activity contours (solid) for plane 12, frame 1 in the range 20–100% of maximum activity signal and isodoses (dashed) in the range 20–100% of total dose.

delivered dose to both the PMMA phantom and the pig leg was 10 Gy at dose maximum (2.5 Gy per field in the pig leg study). The PET acquisition of the PMMA phantom was performed during a total measuring time of 60 min followed by a 15 min 2D transmission scan. The time interval between irradiation on the Racetrack Microtron and the acquisition of the pig leg was 3 min and 46 s. Positron activity measurements were performed during a total emission and transmission time of (60 + 30) min, split into 12 time frames. The duration of the first three frames were 2 min and the remaining nine frames 6 min each. During the pig leg study image fusion was performed using fiducial markers containing radioactivity. Also, by using the transmission rather than emission PET data for image matching, fusion of PET and CT images was easy. In both studies conventional laser alignment of the object in the treatment room as well as in the PET camera was used.

2.5. Data analysis

The PET images in figure 5, the total count rate ${}^{\chi}S_V(t)$ for ${}^{11}\text{C}$, ${}^{13}\text{N}$ and ${}^{15}\text{O}$ defined as the total volume integral of equation (3) and $\text{Tot} S_V(t) = \sum_{\chi} {}^{\chi}S_V(t)$ due to 50 MV photon irradiation of the pig leg, are illustrated for the whole irradiated volume V (s^{-1}). The different decay times allow for radionuclide imaging for the total irradiated volume. By measuring the activity in time frames j , ${}^{\chi}S_V(t)$ can be solved for ${}^{11}\text{C}$, ${}^{13}\text{N}$ and ${}^{15}\text{O}$. For all irradiated volumes V , the count rate ${}^{\chi}S_V(t)$ can be found according to

$$\text{Tot} S_{j,V} = \sum_{\chi} \int_{t_j}^{t_{j+1}} {}^{\chi}S_V(t) \cdot \exp(-\lambda t) dt \quad (4)$$

Figure 5. The measured ($t_s - t_e$) and calculated ($t_0 - t_s$) total, carbon, nitrogen and oxygen count rates (s^{-1}) from measurement on the pig leg in the ECAT EXACT HR scanner. The diagram illustrates the build up of radionuclides in the pig leg during irradiation due to photonuclear reactions and their measured decay in the PET camera. Total irradiation time was 5 min (t_{irr}). The PET measurement started 3 min and 46 s after irradiation treatment was finished (t_s) and ended 60 min later (t_e). PET images for a central section plane 12 are shown for frames 1–3, 12. The experimental data points 1–12 are tabulated in table 2.

where $^{Tot}S_{j,V}$ is the volume and time integral of the measured count rate for all radionuclides $^{Tot}S(t, \mathbf{r})$. The volume V can be chosen arbitrarily within the irradiated volume and does not need to include the entire volume. $^CS_V(t)$, $^NS_V(t)$ and $^OS_V(t)$ are computed by doing a least-square fit, accompanied by additional constraints, which minimizes the sum of the squares of the deviations of the experimental data from equation (4). The number of frames j in equation (4) should at least correspond to the number of activated radionuclides within the object, including all elements that during high energy photon irradiation become positron emitters. In order to derive the radionuclide signal distributions $^XS(t, \mathbf{r})$, we solve the induced positron activity in every small voxel of the irradiated volume V . As all measured PET data are composed of $m \times m$ pixel images for (n planes $\times j$ time frames), the solution vector $[^CS_V(t, \mathbf{r}); ^NS_V(t, \mathbf{r}); ^OS_V(t, \mathbf{r})]$ can be obtained for every position $\mathbf{r}$ (represented by a pixel) in the n planes. The equation is analogous to equation (4) with the exception that $^{Tot}S_j(\mathbf{r})$ is equal to the time integral of the measured signal count rate for all radionuclides $^{Tot}S(t, \mathbf{r})$. Separated PET images $^XS_{j,V}$ are composed by integrating $^XS_j(\mathbf{r})$ over the whole irradiated volume V , $^XS_{j,V} = \int \int \int_V ^XS_j(\mathbf{r}) dV$, representing the signal from activated carbon, oxygen and nitrogen composition within the irradiated tissue due to photonuclear reactions.

3. Results

The production rates of the most abundant positron emitters ^{11}C , ^{13}N and ^{15}O produced during photon irradiation of the pig leg were calculated from the material composition given in table 1 and the cross sections of the photoneutron reactions shown in figure 1. The initial number of target atoms per cm^3 , XN_T , present in the irradiated volume was determined by eye by recognizing tissues in the CT scan and optical image. From table 1, the elemental composition of these tissues could be found and the average elemental composition could be estimated. Our estimation of the average composition of the irradiated volume of the pig

Table 2. Measured total, carbon, nitrogen and oxygen count rates ($\times 10^2$) in s^{-1} acquired from a frozen hind leg of a pig due to 50 MV photon irradiation are compared with predicted count rates shown as the difference in parentheses.

Frame	Start time (min)	End time (min)	Frame duration (min)	$^{\text{Tot}}S_V(t)$ (counts s^{-1})	$^{\text{C}}S_V(t)$ (counts s^{-1})	$^{\text{N}}S_V(t)$ (counts s^{-1})	$^{\text{O}}S_V(t)$ (counts s^{-1})
1	0	2	2	2940 (−9%)	910	135	1890
2	2	4	2	1930 (−5%)	850	117	960
3	4	6	2	1380 (−2%)	795	102	486
4	6	12	6	918 (+2%)	696	78	145
5	12	18	6	637 (+2%)	567	51	19
6	18	24	6	499 (−0%)	463	34	2.5
7	24	30	6	400 (−2%)	377	22	0.32
8	30	36	6	323 (−4%)	308	15	0.1
9	36	42	6	261 (−6%)	251	9.6	<0.1
10	42	48	6	211 (−7%)	205	6.3	<0.1
11	48	54	6	171 (−9%)	167	4.2	≪0.1
12	54	60	6	139 (−10%)	136	2.8	≪0.1
Σ^a				2030 000 (−3%)	1450 000 (−13%)	122 000 (+182%)	460 000 (−21%)

^a Accumulated positron activity for $t = t_s$ to $t = t_e$.

leg was about 30% carbon, 3% nitrogen and 67% oxygen. As described above, treatment execution was performed using four scanned beams, each rotated 90° . However, for the calculation of the radioactive nuclides produced, the time for gantry rotation ($\sim 3 \times 15$ s) has not been included, thus assuming 5 min constant photon irradiation instead of (1 min 5 s irradiation + 15 s gantry rotation) $\times 4$. This will result in a somewhat false and imbalanced predicted and measured nuclide activity distribution.

3.1. Comparison of calculated and measured count rates

The results from the pig leg irradiation expressed as the total, the carbon, nitrogen and oxygen count rates, $^{\text{Tot}}S_V(t)$, $^{\text{C}}S_V(t)$, $^{\text{N}}S_V(t)$ and $^{\text{O}}S_V(t)$, are shown in figure 5 for $t_0 < t < t_e$ for the whole irradiated volume V . For $t_s < t < t_e$, $^{\text{Tot}}S_V(t)$ was derived by integrating the counts $^{\text{Tot}}S(t, \mathbf{r})$ from the activity measurement over the volume irradiated V . Based on $^{\text{Tot}}S(t, \mathbf{r})$, $^{\text{C}}S_V(t)$, $^{\text{N}}S_V(t)$ and $^{\text{O}}S_V(t)$ could be solved from equation (4) which allowed $^{\text{Tot}}S_V(t)$, $^{\text{C}}S_V(t)$, $^{\text{N}}S_V(t)$ and $^{\text{O}}S_V(t)$ to be determined for $t_0 < t < t_s$ using the fact that after the beam is turned off all radionuclides follow their radioactive decay rates. In table 2, measured $^{\text{Tot}}S_V(t)$, $^{\text{C}}S_V(t)$, $^{\text{N}}S_V(t)$ and $^{\text{O}}S_V(t)$ acquired from the total pig leg activity are compared with predicted count rates (difference in parentheses)—based on the estimated elemental composition—using equation (3). For simplicity, the PET camera point spread function was not accounted for in any of these calculations. From the positron activities, determined by the measurement, the composition of the activated nuclides in the irradiated volume of the pig leg was found to be 26% activated carbon, 4% activated nitrogen and 70% activated oxygen.

3.1.1. Error estimation. The combined error in the predicted activity includes errors in calculated photon beam spectra $\Phi_E(E)$, the estimated elemental composition of the pig leg, the photoneutron cross sections obtained from the EXFOR database and the approximate

Figure 6. The total activity distribution and the separated radionuclide activity distributions for oxygen, carbon and nitrogen together with corresponding CT slices for plane selections 12, 18 and 21.

consideration of gantry rotation. The experimental errors include positioning of the phantom at the diagnostic and therapeutic sites by the laser alignment system. The uncertainty is also affected by instrumental errors in the use of the CT scanner, the treatment planning system, the beam uniformity and the PET camera noise, correction and reconstruction algorithms of measured activities. The differences between predicted and measured positron activity in table 2 are probably largely due to the error in the elemental composition estimation of the pig leg. The predicted positron activity originating from the nitrogen component compared to the measured nitrogen activity is overestimated by almost a factor of two, possibly due to experimental noise, while the predicted and measured overall accumulated activity $^{Tot}S_{j,V}$ is almost equal (-3%). Hence, most information is obtained from the nuclides ^{11}C and ^{15}O .

3.2. Radionuclide imaging

The calculation method described in section 2.5 allows the determination of the separate ^{11}C , ^{13}N and ^{15}O signal distributions. The images presented in figure 6 show the total and individual transaxial signal distributions for ^{15}O , ^{11}C and ^{13}N in the selected planes 12, 18 and 21 together with the corresponding CT slices. In figure 5, frame 12 is the last measured activity frame for the central plane 12 and hence a rather good representation of the carbon signal distribution (including noise) since practically all oxygen and nitrogen have decayed. To determine the accuracy of the calculated carbon signal image, a difference image was calculated by subtracting carbon plane 12 in figure 6 from frame 12 in figure 5. This showed a low evenly distributed signal image with a relative mean and standard deviation of $0.6\% \pm 0.11\%$. No significant carbon distributions could be seen, hence the difference image is probably due to statistical noise. However, there is no evidence that the separation technique itself is correct. The carbon-rich tissues such as adipose tissue, lipid and yellow bone marrow are visible in the carbon images in figure 6 and the lack of signal in these regions on the oxygen images is clear. Studying the signal from activated nitrogen in figure 6 and table 2, it is obvious that the error for this component is so large that the true nitrogen signal distribution is not accurately quantified. Since the abundance of nitrogen in tissue (both predicted and measured) is less than 5%, the signal coming from ^{13}N will generally drown in the noise and uncertainties of the oxygen and carbon images.

3.3. Measured PET distributions

The activity profile induced by 50 MV photons in the PMMA phantom is shown in figure 3 together with the profile of the planned absorbed dose distribution. The highest activity should be at the surface and then fall off continuously due to beam attenuation in the phantom. Because of correction and reconstruction algorithms and the spatial resolution losses due to the physical properties of the camera and the positron range, the phantom image shows an anomalous build up of the PET signal near the front surface as seen in the depth profile in figure 3. In fact, the contribution to activity build up from positron distance of flight is very small in comparison to the contribution from detector size, non-collinearity and depth of interaction. However, the influence of positron range can play an important role when positrons from oxygen are imaged in low density tissue such as lung (Sanchez-Crespo *et al* 2004). It is the spatial resolution loss in the PET camera that mainly explains the agreement in figure 3 of the maximum PET signal with the maximum absorbed dose generated by the electrons set in motion by the photons. The maximum PET signal is recorded where the fluence of high energy photons has its maximum, at the periphery of the radiation field at 14.5 cm radius as seen in figure 1 and in the horizontal profile in figure 3. This increased PET signal is mostly due to poor correction and reconstruction algorithms of the PET camera but a slightly higher photon fluence of the radiation field here will contribute a little as well. From PMMA activity simulations using Geant4 (Holmberg 2006), the photon fluence at the field border is 8% higher than at the central axis. The difference between the photon fluence convolved with the photoneutron cross section for the PMMA phantom at the border compared to the central axis is 11%. The difference in the measured PMMA activity image is 35% at depth $z = 2.5$ cm (cf figure 3).

The PET frame 1 (0–2) min, the optical image cut out after treatment, the CT and the planned dose distribution are shown in different combinations in figure 4. Unlike the PMMA phantom, the pig leg tissue composition is far from homogeneous. As seen in previous sections, the activity image distribution will change considerably with time after irradiation. Also density variations within the irradiated volume contribute a great deal to a non-uniform PET profile. But even if density variations can be adjusted by using appropriate CT information, probably no measured activity image in time will at every point be proportional to the dose distribution, whether the PET image is taken early or late after irradiation finish. However, the separation of radionuclide signals and the knowledge about how elements are distributed in the body (cf table 1) can tell us that the carbon distribution is least like the dose distribution and the oxygen distribution most alike. (In fact, the most evenly distributed element in the body is nitrogen.) The progress on these calculations will be discussed in a subsequent paper but in order to do a qualitative comparison of the induced positron activity and the planned dose distribution we used the measured PET frame 1 since it is the one that contains most of the oxygen. PET activity contours (solid) and isodose lines (dashed) are shown together in figure 4(d).

4. Discussion and conclusion

Photonuclear reactions induced in body tissue by high energy bremsstrahlung beams result in positron-emitting radionuclides that can be imaged with a PET camera. In this study, the possible use of PET imaging following high energy photon therapy has been tested on tissue equivalent phantoms with the intention to monitor the delivered dose distribution. Oxygen, which constitutes about 2/3 of the total elemental composition in soft tissue, will dominate the PET signal in measurements taken a few minutes after the photon irradiation due to the

short physical half-life of ^{15}O and its high production cross section. Thus, it is of paramount importance that PET activity measurements start as soon as possible after producing the activity in order to extract most information from the oxygen signal and determine the dose to soft tissue. However, some tissues such as adipose tissue are very carbon rich and for complete information of the delivered dose distribution early activity measurements may not be sufficient. As time elapses the activity image distribution will change considerably with time post-treatment and a perfect agreement between dose and activity is probably impossible to find. In addition, tissue density variations will make the PET images even more irregular but could probably be adjusted by appropriate CT information. However, the fact that measured PET images change with time as a result of the different decay times of the radionuclides will help us to find the separated radionuclide signal distribution. These separated distributions will be a part of a scaling factor for nuclide composition similar to the way CT will be for electron density.

The absorbed dose distribution is partly a build-up phenomenon determined by the secondary electrons set in motion by the photons, while the PET signal represents the tissue activation induced by the local high energy photon fluence. The absorbed dose when using non-uniform photon beams can be calculated by convolving the primary photon fluence distribution differential in energy with the point energy deposition kernel for a specific medium and photon energy (Ahnesjö *et al* 1987). In modern treatment planning such energy deposition kernels are taken from pre-calculated libraries to quickly and accurately calculate the absorbed 3D dose for complicated geometries and intensity-modulated beams. A similar convolution formalism can be used in PET imaging where the measured count rate of the generated activity distribution is estimated by folding the activity density distribution with the point spread function of the PET camera. To do PET-CT dose delivery verifications in the future, the pre-calculated PET image should be compared with the measured activity after treatment. The goal is to do this type of dose delivery verification during the early and sometimes later fractions too, in order to correct for possible errors in beam set-up, patient positioning, treatment planning and local changes in the patient anatomy.

This study indicates the great value of a combined radiotherapy-PET-CT so-called diagnostic treatment unit. With an RT-PET-CT unit a high signal could be collected at a much lower dose level than used in these experiments. Since almost three-quarters of the oxygen was lost before reaching the PET camera, an online PET solution would also reduce the acquisition time considerably. Real patient dose delivery verification by means of PET imaging seems to be applicable provided that biological transport processes such as capillary blood flow containing mobile ^{15}O and ^{11}C in the activated tissue volume can be accounted for. Considering the PET camera, the resolution has to be reduced and the fact that organs will move during imaging must be corrected for by using respiratory and cardiac triggering.

Acknowledgments

This work has received research funding from VINNOVA Center of Excellence and The Cancer Society in Stockholm. Irena Gudowska and Bo Nilsson are acknowledged for helpful discussions on photonuclear reactions and dosimetry issues. The authors would like to thank all the personnel at Karolinska University Hospital and Karolinska Institutet for their help and assistance in CT scanning, treatment planning, radiation treatment and PET measurements, Brigida da Costa Ferreira, Aleksandra Zapotoczna, Per-Olof Schnell, Professor Stig Larsson,

Lars Johansson, Professor Martin Ingvar and Julio Gabriel. We also acknowledge the work done by Eric Nolf in developing the open source medical image conversion utility and library XMedCon, <http://xmedcon.sourceforge.net>, and are grateful to Professor Marilyn E Noz at the Department of Radiology, New York University, for helpful discussions in this work.

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