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Short-lived positron emitters in beam-on PET imaging during proton therapy

P Dendooven¹, H J T Buitenhuis¹, F Diblen^{1,3},
P N Heeres¹, A K Biegun¹, F Fiedler⁴, M-J van Goethem²,
E R van der Graaf¹ and S Brandenburg¹

¹ KVI-Center for Advanced Radiation Technology, University of Groningen, Zernikelaan 25, 9747AA Groningen, The Netherlands

² University of Groningen, University Medical Center Groningen, Department of Radiation Oncology, PO Box 30001, 9700 RB Groningen, The Netherlands

³ MEDISIP, Department of Electronics and Information Systems, Ghent University-iMinds Medical IT-IBiTech, De Pintelaan 185 Block B, B-9000 Ghent, Belgium

⁴ Helmholtz-Zentrum Dresden—Rossendorf, Institute of Radiation Physics, PF 510119, 01314 Dresden, Germany

E-mail: p.g.dendooven@rug.nl

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Abstract

The only method for *in vivo* dose delivery verification in proton beam radiotherapy in clinical use today is positron emission tomography (PET) of the positron emitters produced in the patient during irradiation. PET imaging while the beam is on (so called beam-on PET) is an attractive option, providing the largest number of counts, the least biological washout and the fastest feedback. In this implementation, all nuclides, independent of their half-life, will contribute. As a first step towards assessing the relevance of short-lived nuclides (half-life shorter than that of ^{10}C , $T_{1/2} = 19\text{ s}$) for *in vivo* dose delivery verification using beam-on PET, we measured their production in the stopping of 55 MeV protons in water, carbon, phosphorus and calcium. The most copiously produced short-lived nuclides and their production rates relative to the relevant long-lived nuclides are: ^{12}N ($T_{1/2} = 11\text{ ms}$) on carbon (9% of ^{11}C), ^{29}P ($T_{1/2} = 4.1\text{ s}$) on phosphorus (20% of ^{30}P) and $^{38\text{m}}\text{K}$ ($T_{1/2} = 0.92\text{ s}$) on calcium (113% of $^{38\text{g}}\text{K}$). No short-lived nuclides are produced on oxygen. The number of decays integrated from the start of an irradiation as a function of time during the irradiation of PMMA and 4 tissue materials has been determined. For (carbon-rich) adipose tissue, ^{12}N dominates up to 70 s. On bone tissue, ^{12}N dominates over ^{15}O during the first 8–15 s (depending on carbon-to-oxygen ratio). The short-lived nuclides created on phosphorus and calcium provide 2.5 times more beam-on PET counts than the long-lived ones.

produced on these elements during a 70 s irradiation. From the estimated number of ^{12}N PET counts, we conclude that, for any tissue, ^{12}N PET imaging potentially provides equal to superior proton range information compared to prompt gamma imaging with an optimized knife-edge slit camera. The practical implementation of ^{12}N PET imaging is discussed.

Keywords: proton therapy, monitoring, positron emission tomography, nitrogen-12

(Some figures may appear in colour only in the online journal)

1. Introduction

In comparison to photon radiotherapy, particle beam radiotherapy (mainly protons and carbon ions are used) generally results in a lower radiation dose to co-irradiated normal tissues due to the superior dose deposition properties of particles: a well-defined, finite penetration depth in matter and a high dose deposition close to the end of the trajectory (the Bragg peak). Depending on the details of tumor location and size, a smaller dose to normal tissues may significantly reduce long-term complications and thus increase the quality of life of patients. However, these benefits of particle beam radiotherapy come with a consequence: as compared to photons, the precise dose deposition entails increased sensitivity to anatomical changes in the patient, ion range uncertainties and treatment errors such as patient setup errors. For these reasons, an *in vivo* technique to verify the dose delivery is key to fully translating the superior dose deposition of particles into a clinical benefit. Since the particles stop inside the patient, *in vivo* dose delivery verification requires imaging of secondary radiation. High-energy photons created by nuclear interactions of the beam particles with the atomic nuclei in the irradiated tissue are suitable for this purpose: their interaction with human tissue is rather weak and they are relatively easily detected by suitable instruments. Two types of photons are available: positron annihilation photons (511 keV) following the decay of positron emitting nuclides and prompt gamma rays emitted on a sub-nanosecond timescale in the decay of excited atomic nuclei. For an overview of this subject, especially related to proton beam radiotherapy, which is considered in the current work, we refer to the recent reviews by Studenski and Xiao (2010), Parodi (2011), Fiedler *et al* (2012), Zhu and El Fakhri (2013), Knopf and Lomax (2013) and Kraan (2015). A non-nuclear technique for range verification could be based on the detection of ultrasound generated by the thermoacoustic effect (see e.g. Hayakawa *et al* 1995, Assmann *et al* 2015).

Presently, the only method that is sufficiently developed for routine clinical use is the imaging of positron annihilation photons using positron emission tomography (PET). The time delay between the production of a positron emitting nucleus by the therapeutic beam and the actual emission of the positron (the average delay being the radioactive decay time constant) represents a fundamental drawback for dose delivery verification by means of PET. The most copiously produced positron emitters, ^{15}O , ^{11}C , ^{30}P and ^{38}K , have radioactive decay half-lives between 2 and 20 min, comparable to or longer than the typical duration of a therapeutic irradiation. Consequently, as an image acquisition of at least a few minutes is required to obtain a sufficient number of PET counts, instantaneous feedback is precluded. Also, verification of the delivery of a field is hampered by the residual radioactivity produced during the delivery of previous fields. Furthermore, the relatively long acquisition time leaves room for biological washout resulting in a loss of PET activity and a smearing out of the PET image, thereby reducing the value of the PET images.

The drawbacks related to the delayed nature of PET have prompted the development of prompt gamma ray imaging which allows in principle immediate feedback on the dose delivery, is not influenced by biological washout and does not suffer from previously produced radioactivity (assuming the energy threshold of the detection system is set above 511 keV). Additionally, due to a lower reaction energy threshold, the prompt gamma ray spatial distribution extends 5–10 mm closer to the distal edge of the Bragg peak than the positron emitter distribution. Technically, prompt gamma imaging is challenging due to the high energy of the gamma rays to be imaged, up to about 7 MeV (see e.g. Polf *et al* 2009b), and the large neutron flux during irradiation, potentially generating signals that are not in a useful way related to the proton range (Biegun *et al* 2012, Verburg *et al* 2013). Prompt gamma imaging instruments of various nature are under development: ‘traditional’ Compton cameras (Llosá *et al* 2013, Hueso-Gonzalez *et al* 2014, Krimmer *et al* 2015, McCleskey *et al* 2015); electron-tracking Compton cameras (Kurosawa *et al* 2012); collimated cameras (Min *et al* 2012, Smeets *et al* 2012, Perali *et al* 2014, Verburg *et al* 2014); gamma-electron vertex imaging (Kim *et al* 2012); prompt gamma timing (Golnik *et al* 2014). Results of prompt gamma ray imaging during patient irradiations are yet to be published; the clinical usefulness of prompt gamma ray imaging thus remains to be determined. Closest to clinical implementation is the knife-edge slit camera developed by Smeets *et al* (2012) and Perali *et al* (2014). In irradiations of homogeneous PMMA targets with pencil beams and using a calibration via Monte Carlo simulations, Smeets *et al* (2012) achieve a 1–2 mm precision (1σ) for the range estimation with numbers of protons that correspond to doses in water at the Bragg peak of 15 cGy at 100 MeV and 25 cGy at 160 MeV proton energy. Perali *et al* (2014) reach a precision (2σ) in range shift retrieval of 4 mm with 0.5×10^8 , 1.4×10^8 and 3.4×10^8 protons at 100, 160 and 230 MeV, respectively, concluding that ‘the acquisition of prompt gamma profiles for *in vivo* range verification of proton beam with the developed gamma camera and a slit collimator is feasible in clinical conditions’.

PET imaging during an irradiation while the beam is on (so called beam-on PET) is an attractive implementation of PET for *in vivo* dose delivery verification: it provides the largest number of counts, is the least susceptible to biological washout and allows the fastest feedback on dose delivery. Scanners presently installed *in situ* (close to the patient during irradiation, see e.g. Miyatake *et al* 2010) cannot take high-quality data while the therapeutic beam is on due to the large prompt radiation flux. Consequently, data is taken only after an irradiation (potentially also in-between fields) in the case of a cyclotron beam, while at a synchrotron, data is taken in-between the beam spills, possibly continued after a field or an irradiation is completed (see e.g. Enghardt *et al* 2004, Parodi *et al* 2005). With pencil beam scanning, PET data free from prompt radiation background can be taken in-between spots and in-between energy planes, representing an acquisition time that is a significant fraction of the total duration of an irradiation.

In the clinical use of PET at proton therapy facilities up to now, nuclides with a half-life shorter than that of ^{10}C ($T_{1/2} = 19\text{ s}$) contribute very little to PET imaging after the irradiation. However, in a beam-on implementation, all PET nuclides, independent of their half-life, will contribute to the image, with the shorter-lived ones contributing more (relative to the production rate). For the purpose of the present work, we define ‘short-lived nuclides’ to be nuclides with a half-life shorter than that of ^{10}C .

The short-lived positron emitters ^{13}O , ^{12}N and ^8B have been mentioned in relation to carbon ion therapy. Based on the simulations by Pönisch *et al* (2004), Crespo *et al* (2005) state that, in irradiations of a PMMA target, ^{12}N and ^8B are the most abundant and deduce from experiment a relative contribution of these nuclides of 9.9% and 2.1% of the total number of annihilation events. Some image blurring due to the high positron endpoint energy of these nuclides has

been observed. Parodi *et al* (2008) mention that in-beam random suppression techniques, as discussed by Crespo *et al* (2005), will enable the detection of these short-lived positron emitters (note that in relation to synchrotron irradiations, the term in-beam imaging has been used to refer to imaging in-between as well as during beam spills, the latter being termed beam-on imaging in this paper). Both Crespo *et al* (2005) and Parodi *et al* (2008) do not identify these positron emitters nor evaluate their impact because of the lack of experimental information.

Miyatake *et al* (2010) measured the decay curves of positron emitter activity after therapeutic proton irradiation in five patients for each of the following tumour sites: head and neck, liver, lung and prostate. In the head-and-neck and prostate cases, short-lived components with half-lives of 2.6 ± 1.5 s and 1.5 ± 0.4 s respectively, were observed (the uncertainties on the half-life values reflect the variation across the five patients investigated). These components have been interpreted to be due to the production of ^{38}Ca ($T_{1/2} = 439$ ms) and ^{39}Ca ($T_{1/2} = 860$ ms) on calcium. It is important to note that at the end of the irradiation, the short half-life component represents on average 19% of the total activity for the head-and-neck cases and 37% for the prostate cases. However, over the 200 s PET scan after the end of the irradiation, ^{15}O is dominating.

Shao *et al* (2014) present results of an initial phantom study using a small *in situ* PET system at a synchrotron, demonstrating the feasibility of including PET data obtained during beam spills. A possible effect of short-lived nuclides is mentioned but not investigated.

In the development of a beam-on PET scanner by Sportelli *et al* (2014) and Kraan *et al* (2014), short-lived nuclides are considered. The high positron endpoint energy of these nuclides results in a broad positron range distribution that degrades the PET image spatial resolution. The simulation by Kraan *et al* (2014) of a 2 min irradiation of PMMA with 62 MeV protons includes the production of ^8B , ^{12}N and ^{13}O , showing fractions of the total PET nuclide decays during the irradiation of 8.4%, 4.8% and 0.8%, respectively. A slight increase in the tails of the 1D activity profiles due to the very short-lived nuclides is seen in the simulation results.

The consideration of short-lived ($T_{1/2} < 19$ s) positron emitters in the developments reviewed above suffers from the fact that there is essentially no experimental information concerning their production. Such knowledge is essential to assess the feasibility of the beam-on implementation of *in vivo* dose delivery verification using PET. The short-lived positron emitters are relevant if they allow verification on a time scale much shorter than the duration of an irradiation or if they degrade the spatial resolution of the PET images due to positron range blurring. In the experiments discussed here, the integrated production of positron emitters during the stopping of 55 MeV protons in water, carbon, phosphorus and calcium has been measured. We identify experimentally for the first time which short-lived positron emitters are produced in sufficient quantities to be relevant for the beam-on implementation of PET-based *in vivo* dose delivery verification of proton therapy. We compare ^{12}N PET imaging with state-of-the-art prompt gamma imaging at the level of the number of counts detected.

2. Materials and methods

2.1. General considerations

The purpose of the experiments discussed here was to determine which, if any, short-lived positron emitters are relevant for PET-based *in vivo* dose delivery verification. We consider that, in order to be relevant, production has to be significant at rather low proton energy; nuclides produced at high energy are produced far from the distal edge of the irradiation and are thus of limited relevance. Also, detailed knowledge of the energy dependence of the cross section is not needed to decide on the relevance. We therefore measured the energy-integrated production

of short-lived positron emitters for a relatively low-energy proton beam. Sufficiently relevant nuclides will then warrant a more detailed follow-up investigation.

The elements in the human body relevant for the production of positron emitters are carbon, nitrogen, oxygen, phosphorus and calcium, with carbon and oxygen being the most important ones. Nitrogen has not been considered as a target material in this work because: (1) nitrogen is in any tissue much less abundant than both carbon and oxygen; (2) the same positron emitters are produced on nitrogen as on carbon and oxygen; (3) the cross sections for the production of the long-lived ^{13}N and ^{11}C nuclides on nitrogen are of the same magnitude as for their production on ^{16}O and ^{12}C (EXFOR 2015) and we consider it unlikely that this would be different for short-lived nuclides. Although, in bone tissue, phosphorus has about the same atomic density as nitrogen and calcium has up to twice this value, phosphorus and calcium are relevant elements as they lead to different positron emitters than carbon and oxygen.

Based on the above considerations, we determined the integral production of short-lived positron emitters in the stopping of 55 MeV protons in carbon, oxygen, phosphorus and calcium. The production of the well-known longer-lived nuclides was measured as well in order to assess the relevance of the short-lived nuclides. Table 1 lists the PET nuclides, both short- and long-lived, investigated in this work together with some of their characteristics.

2.2. General method

The production of a positron emitter can be deduced from a measurement of its decay radiation provided that the decay radiation can be uniquely attributed to that particular positron emitter. Gamma-rays are very well suited for this as, in a particular experiment, their energy is almost always unambiguously related to one nuclide. However, as shown in table 1, the nuclides of relevance for this work do not all emit gamma rays and the gamma rays that are emitted are often of high energy and/or have a small branching ratio. They are thus difficult to detect with high efficiency. As an alternative, the production of positron emitters is determined from the intensity of the 511 keV positron annihilation photons that follow the radioactive decay of a positron emitter. Different nuclides are identified based on their half-life. In order to do this, the proton beam is pulsed: it is delivered as a succession of beam-on and beam-off periods. Only the beam-off period, during which the nuclei that were previously created are decaying, is used in the analysis because the presence of prompt gamma radiation during the beam-on period adds a large background to the measurement of the 511 keV photons. Sufficient counting statistics are obtained by summing a (large) number of beam-on/off cycles.

2.3. Data analysis

The decay of the 511 keV intensity during the beam-off period is fitted with the sum of one or more exponential decays and, if relevant, a constant background (see section 3.1). If data is accumulated and the time spectra summed over K beam-on/beam-off cycles, the number of nuclei produced per second during beam on, P , is given by:

$$P = A_0 \left[(1 - e^{-\lambda T}) \sum_{m=0}^{K-1} (K - m) e^{-\lambda m 2T} \right]^{-1} \quad (1)$$

with λ the decay constant, T the duration of the beam-on and off periods (we used a symmetric cycle with beam-on and beam-off periods both equal to T) and A_0 the activity at the beginning of the beam-off period. In order to have a good nuclide identification based on the half-life,

Table 1. Positron emitters considered in this work, potentially produced by protons on carbon, oxygen, phosphorus and calcium.

Positron emitter	Half-life	Gamma ray decay data	
		Energy (keV)	Branching ratio (%)
⁸ B	770 ms		No γ
⁹ C	127 ms		No γ
¹⁰ C	19.3 s	718	100
¹¹ C	1223 s		No γ
¹² N	11.0 ms	3215 4439	2.7 4.8
¹³ N	598 s		No γ
¹³ O	8.58 ms		No γ
¹⁴ O	70.6 s	2313	99.4
¹⁵ O	122 s		No γ
²⁹ P	4.14 s	1273	1.32
³⁰ P	150 s	2235	0.059
³⁰ S	1.18 s	677	78.4
³¹ S	2.58 s	1266	1.09
³⁷ K	1.22 s	2796	2.04
^{38g} K	456 s	2168	99.9
^{38m} K	924 ms		No γ
³⁸ Ca	439 ms	1568	20
³⁹ Ca	860 ms	2522	0.0025

Note: Gamma ray decay data for the most intense gamma ray lines are given. Data taken from NNDC (2015).

T is chosen to be about 5 times the half-life of the short-lived nuclide being investigated. For $T \approx 5 T_{1/2}$, all terms other than $m = 0$ are negligible, so equation (1) becomes:

$$P = \frac{A_0}{K(1 - e^{-\lambda T})} \quad (2)$$

and only the beam-on period immediately preceding each beam-off period contributes to the observed decays. In many measurements, contributions from longer-lived nuclides are present; to deduce their production rate, a sufficient number of terms from equation (1) was taken into account.

It should be noted that in the formulae above, P is assumed to be constant during a measurement, a condition quite well fulfilled because of the stability of the beam intensity during the irradiations. Finally, the number of nuclei produced per proton is given by:

$$N_{\text{nuclei}} = \frac{P K T}{N_p} \quad (3)$$

with N_p total number of protons in the measurement.

2.4. The effect of escaping positrons

If a positron emitter decays within a distance from the edge of the target that is comparable with the average range of its positrons, a sizeable fraction of positrons will leave the target. These positrons do not annihilate in the target and thus do not contribute to the number

Figure 1. Picture of the experimental setups: left: first experiment, right: second experiment. 1: germanium clover detector, 2: anti-Compton shield, 3: beam ionization monitor, 4: target, 5: lead shielding. The target and the horizontally installed detector shown in the right picture were used for another purpose than the investigation of short-lived positron emitters.

of detected annihilation photons. If this effect is not counteracted or taken into account, it will lead to an underestimation of production rates. As the positron endpoint energy typically increases with decreasing half-life, the effect of escaping positrons will be larger for shorter half-lives. The shortest-lived nuclides investigated in this work have maximum positron ranges that are comparable with the range of the 55 MeV protons used. For these nuclides a substantial escape effect is thus expected.

In sections 3.1.1–3.1.7, we analyze the production of positron emitters without taking the effect of escaping positrons into account. In section 3.1.8, we calculate the effect of escaping positrons and perform a correction to the results.

2.5. Irradiation and detector setup

The experiments were performed at the irradiation facility of the AGOR cyclotron at the KVI-Center for Advanced Radiation Technology (KVI-CART), University of Groningen. Two separate experiments were performed. The experimental set-ups are shown in figure 1.

After passing through the beam line vacuum window, the proton beam passes through the beam ionization monitor (BIM), an air ionization chamber. Before the experiment, the conversion from BIM output charge (expressed in monitor units) to number of protons was determined. The number of monitor units was integrated during an irradiation to determine the total number of protons.

The target was installed about 30 cm downstream from the BIM. The full width of the beam on target was about 15 mm as measured with Gafchromic EBT2 film. In the first experiment, graphite and water targets were used; in the second experiment, phosphorus and calcium targets were used, and, in order to allow a cross check between the two experiments, a graphite target was irradiated as well. Some relevant information on the targets is given in table 2. All targets are thick enough to stop 55 MeV protons and have a large enough transverse size to capture the full beam.

The 511 keV annihilation photons are detected by a germanium clover detector consisting of 4 individual germanium detection crystals; for details see Duchêne *et al* (1999) and Elekes *et al* (2003). The measurement of the production of short-lived positron emitters was only part

Table 2. Target properties.

Target	Target thickness (g cm ⁻²)	Target form	Range 55 MeV protons ^a (g cm ⁻²)
Graphite	4.3	50 mm square, 25 mm thick	2.97
Water	5	Thin-walled polystyrene cup	2.64
Phosphorus	5.4	Red phosphorus powder pressed into a 30 mm diameter plastic container	3.50
Calcium	4.3	Powder pressed into a 30 mm diameter plastic container	3.85

^a From NIST (2015).

of the aim of the experiments. Due to different overall requirements of these experiments, the clover detector installation was not identical for the two experiments. In the first experiment, the clover detector was rather heavily shielded inside its anti-Compton shield and additional lead bricks (see figure 1, left). Using a ²²Na source, a 3% loss of 511 keV counts was measured when operating the detector in anti-Compton mode as opposed to not using the anti-Compton shield. This difference was taken into account in the data analysis of the measurements performed in anti-Compton mode. The detector was placed horizontally with respect to the target, the distance from the proton beam to the detector front endcap being 25 cm. In the second experiment, the clover detector is installed without anti-Compton shield or other shielding, hanging above the target with a distance of 48 cm between the proton beam and the detector front endcap (see figure 1, right).

The energy signals from the 4 germanium crystals in the clover detector were carefully gain-matched by fine-tuning the individual spectroscopy amplifiers and summed in an analog way, providing an energy signal in so-called add-back mode. In this way, an effectively larger detector volume is created, giving a full-energy efficiency larger than the sum of the efficiencies of the individual germanium crystals. For the relatively low energy of 511 keV, the increase in full-energy efficiency in add-back mode of about 20% (Elekes *et al* 2003) is however rather modest. During the first experiment, one germanium crystal did not function properly so the experiment was performed with summing the signals from 3 crystals. In the second experiment, all 4 germanium crystals were functioning properly and thus summed.

The summed energy signal was put through a single-channel analyzer generating a logic pulse each time the detected energy was in a narrow energy window set around 511 keV. Some of the counts within the energy window are background under the 511 keV full-energy peak and a correction for this is needed to calculate the positron emitter production. The peak-to-total ratio inside the 511 keV energy window depends on the gamma ray energy spectrum that is being observed and is thus, to some extent, different for each measurement. It can be determined from the summed energy spectrum gated by the single-channel analyzer output pulse. Such spectra were not recorded during the measurements. However, in the beam-off periods, the positron annihilation photons are the main contribution to the gamma ray spectrum. Therefore, we determined the peak-to-total ratio inside the 511 keV energy window using a ²²Na source whose gamma ray spectrum is a good surrogate for that during the measurements. This ratio was determined to be 0.88 in the first experiment and 0.95 in the second experiment. These values are compatible with the non-gated gamma ray spectra that were recorded during the beam-off periods for some of the measurements.

The efficiency for the full-energy detection of 511 keV photons was measured by placing a calibrated ²²Na source at the target position. This efficiency was determined to be $1.42(2) \times 10^{-3}$ in the first experiment and $7.67(3) \times 10^{-4}$ in the second experiment. The

uncertainties given are statistical uncertainties on the measured peak intensity only. The uncertainty of the ^{22}Na source activity calibration adds a systematic uncertainty of 3%.

The logic output of the single-channel analyzer was sent to an ORTEC Multi-Channel Scaler (MCS) to record the time spectrum of the 511 keV photons. The MCS pass length (the total duration of the time spectrum, after which the MCS starts adding counts from the beginning of the spectrum again) was set equal to the desired beam pulsing period. The ‘mid pass out’ functionality of the MCS was used to generate beam-on and off periods of equal duration by letting it control electrostatic deflection plates in the cyclotron injection beam line.

For several combinations of target and beam pulse duration, the gamma-ray spectrum, using only one germanium crystal, was measured during the beam-off periods. This provides extra information on the type and intensity of positron emitters produced. In general, the extra information is limited because (1) quite a number of positron emitters relevant for this study do not emit gamma rays or only with very small branching ratios, (2) the gamma rays emitted with high branching ratio are often of high energy, leading to a small and difficult to determine detection efficiency. Whenever relevant, results from the beam-off gamma ray spectra are mentioned in sections 3.1.1–3.1.7. Table 1 gives the relevant gamma ray information.

Proton beam intensities were chosen low enough, about 0.1 nA, that data acquisition dead-time and random summing during the beam-on period did not prevent recording high-quality gamma ray spectra. As the MCS data relate to the beam-off period when gamma ray emission from the target is much smaller, neither dead-time nor random summing corrections are needed.

3. Results

3.1. Measured production of positron emitters

In this section, the production of the positron emitters observed for the different targets and beam pulse durations is discussed. The main results are derived from the MCS time spectra. Weighted least-square fits using a relevant combination of one or more exponential decays and, occasionally, a constant background, are performed. The weights are taken equal to the square root of the number of counts in the time spectrum channels. Where relevant, information from the gamma-ray spectra taken during the beam-off period is mentioned. For all nuclides considered, the positron emission branching ratio is virtually 100%, so no correction for branching ratio is needed. The effect of the escape of positrons from the target is considered in section 3.1.8. The results are summarized in table 4.

3.1.1. The production of ^{14}O on ^{16}O . The production of ^{14}O ($T_{1/2} = 70.6\text{ s}$) on ^{16}O is investigated with the water target and 200 s on/200 s off beam pulsing. The MCS spectrum of the 511 keV intensity versus time during the beam-off period is shown in figure 2, left. The spectrum shows no evidence of the presence of ^{14}O ; it is dominated by the decay of ^{15}O . Additionally, contributions from both ^{13}N and ^{11}C are to be expected. Due to the fact that the beam pulse duration is several times smaller than the half-lives of both ^{13}N and ^{11}C , the individual contributions from these two nuclides cannot be determined: adding two long-lived components to the ^{15}O decay leads to a fit in which one of these components has a negative contribution. Adding only one of the long-lived components to the ^{15}O decay gives the smallest reduced χ^2 value for the $^{13}\text{N} + ^{15}\text{O}$ combination, $\chi^2 = 2.28$ versus $\chi^2 = 2.41$ for the $^{11}\text{C} + ^{15}\text{O}$ combination. The fit with the $^{13}\text{N} + ^{15}\text{O}$ combination is shown in figure 2, left. This indicates that the contribution from ^{13}N is somewhat larger than that of ^{11}C . This can be understood from

Figure 2. Time spectrum of the 511 keV intensity during the beam-off period for a water target and 200 s on/200 s off beam pulsing (left) and for a graphite target and 100 s on/100 s off beam pulsing (right). The result of the fit considering the decay of the nuclides indicated as well as the individual contributions as deduced from the fit (thin lines) are shown.

the respective cross sections below 55 MeV: the production of ^{11}C on ^{16}O has a high energy threshold of 27.5 MeV and reaches its maximum only at a proton energy of about 65 MeV. The production of ^{13}N on ^{16}O has a low energy threshold of 5.7 MeV and several sizeable resonances below 20 MeV. As neither ^{13}N nor ^{11}C emit gamma rays, the gamma ray spectrum does not help in disentangling these respective contributions.

The gamma ray spectrum taken during the beam-off periods (figure 3) shows a contribution of ^{14}O : a 2313 keV peak intensity of 298 ± 21 counts. From Elekes *et al* (2003), the detection efficiency for this peak is estimated to be $2.3 \pm 0.5 \times 10^{-5}$. The calculated ^{14}O production of 6.9×10^{-5} per proton is, within uncertainties, the same as the uncertainty on the ^{15}O production deduced from the 511 keV time spectrum and thus explains why ^{14}O is not observed in the time spectrum. The small contribution of ^{14}O is compatible with the cross section information (JANIS 2012, p 44): the reaction threshold is rather high, close to 25 MeV, and the maximum of the cross section, around 50 MeV, is between 1 and 2 mb.

3.1.2. The production of ^{10}C . The data discussed in section 3.1.1 show no evidence for the production of ^{10}C ($T_{1/2} = 19.3$ s) on oxygen. The production of ^{10}C on ^{12}C was investigated with a graphite target and 100 s on/100 s off beam pulsing. The MCS spectrum of the 511 keV intensity versus time during the beam-off period is shown in figure 2, right. The only longer-lived nuclide that is expected to contribute to this spectrum is ^{11}C . The figure shows that a fit considering only the decay of ^{10}C and ^{11}C describes the data very well and gives no evidence of other contributions.

3.1.3. The production of ^8B . The production of ^8B ($T_{1/2} = 0.770$ s) will be the highest on ^{12}C ; we thus investigated the graphite target with 4 s on/4 s off beam pulsing. The MCS spectrum of the 511 keV intensity versus time during the beam-off period is shown in figure 4, left. The first point in the spectrum (at a time of 0.1 s) is not taken into account as it contains a contribution from ^{12}N (see section 3.1.5); ^9C will not contribute to the spectrum, see section 3.1.4. Based on the results from section 3.1.2, the contribution of both ^{10}C and ^{11}C need to be considered.

Figure 3. Gamma ray spectrum taken during the beam-off periods of the water target irradiation with 200s on/200s off beam pulsing. The spectrum intensity is dominated by the 511 keV annihilation radiation. The peak from the decay of ^{14}O at 2313 keV is clearly observed. All other major peaks are due to the activation of beam line components or natural background.

Figure 4. Time spectrum of the 511 keV intensity during the beam-off period for 4s on/4s off (left) and 700ms on/700ms off (right) beam pulsing on a graphite target. The result of the fit considering the decay of the nuclides indicated as well as the individual contributions as deduced from the fit (thin lines) are shown. The first data point(s) which contain a contribution from the short-lived ^{12}N is (are) excluded from the fitting procedure.

Figure 5. Time spectrum of the 511 keV intensity during the beam-off period for water (left) and graphite (right) targets and a 60 ms on/60 ms off beam pulsing. The result of the fit considering a constant (thin line) plus a decay with a 10 ms half-life (left) or the decay of ^{12}N (right) (thick line) is shown.

Indeed, the best fit is obtained with both of these nuclides included. Due to the long half-life of ^{11}C relative to the beam pulsing, its contribution is represented by a constant in the fit.

3.14. The production of ^9C . As the production of ^9C ($T_{1/2} = 127$ ms) will be highest on ^{12}C , it is investigated with the graphite target. A 700 ms on/700 ms off beam pulsing is used. The MCS spectrum of the 511 keV intensity versus time during the beam-off period is shown in figure 4, right. The first few points in the spectrum (up to a time of 40 ms) are not taken into account as they contain a contribution from ^{12}N (see section 3.1.5). Contributions from long-lived nuclides can be assumed constant over the short cycle, so the spectrum is fitted with the decay of ^9C on top of a constant. A statistically barely relevant result follows: the number of counts of ^9C in the first channel of the time spectrum is 81 ± 47 . We conclude that ^9C is not definitely observed, and calculate an upper limit using a value of the above-mentioned fit parameter of about 130 (the value plus 1σ uncertainty).

3.15. The production of ^{12}N and ^{13}O . The half-lives of ^{12}N ($T_{1/2} = 11.00$ ms) and ^{13}O ($T_{1/2} = 8.58$ ms) are so close that one needs to consider the two nuclides simultaneously. On the water target, both of these nuclides can be produced. Figure 5, left, shows the MCS spectrum of the 511 keV intensity versus time during the beam-off period using 60 ms on/60 ms off beam pulsing. No clear short-lived contribution is seen. Clearly, fitting the spectrum with separate ^{12}N and ^{13}O contributions does not make sense. A fit with a 10 ms decay (as an average of the ^{12}N and ^{13}O half-lives) on top of a constant was performed to estimate the total contribution of both nuclides. The resulting contribution, expressed as the number of counts in the first channel of the time spectrum, is 92 ± 68 counts. We conclude that neither ^{12}N nor ^{13}O are definitely observed, but we calculate an upper limit using a value of the above-mentioned fit parameter of about 150 counts.

On carbon, protons cannot produce ^{13}O . The data from the graphite target with 60 on/60 ms off beam pulsing is thus analyzed considering only ^{12}N . All other contributing nuclides have a half-life much longer than the beam pulsing, so they are represented by a constant. Figure 5, right, shows, for the first experiment, the MCS spectrum of the 511 keV intensity versus time during the beam-off period as well as the results of a fit with the decay of ^{12}N on top of a

Figure 6. Time spectrum of the 511 keV intensity during the beam-off period for a phosphorus target and 20 s on/20 s off beam pulsing (left) and a calcium target and 5 s on/5 s off beam pulsing (right). The result of the fit considering the decay of the nuclides indicated as well as the individual contributions as deduced from the fit (thin lines) are shown.

constant. An identical irradiation was performed during the second experiment, resulting in a $22 \pm 4\%$ (statistical uncertainty only) lower ^{12}N production. The origin of this difference is not understood. This difference, however, has no implications for the results of this work, i.e. the assessment which short-lived positron emitters are relevant for proton therapy treatment verification in beam-on PET

3.1.6. Production on the phosphorus target. The production of ^{29}P is investigated with the phosphorus target and 20 s on/20 s off beam pulsing. The MCS spectrum of the 511 keV intensity versus time during the beam-off period is shown in figure 6, left. In the gamma ray spectrum measured during the beam-off period, a contribution from ^{30}S ($T_{1/2} = 1.18$ s) is seen. As the most intense gamma ray emitted in the ^{31}S decay ($T_{1/2} = 2.58$ s), at an energy of 1266 keV, has a branching ratio of only 1.09%, the fact that this gamma ray is not observed does not allow to exclude a contribution from ^{31}S . The beginning of the spectrum decreases somewhat faster than the 4.1 s half-life of ^{29}P and fits with a contribution from either ^{30}S or ^{31}S show a clearly reduced χ^2 value (1.4 versus 2.0). Adding both sulfur nuclides leads to a fitted negative contribution from ^{31}S ; ^{30}S thus seems to be the dominant of these two sulfur nuclides, a conclusion compatible with the gamma-ray spectrum.

3.1.7. Production on the calcium target. The production of ^{38g}K ($T_{1/2} = 7.6$ m) on calcium is well known. The most likely short-lived nuclides produced are ^{38m}K ($T_{1/2} = 925$ ms), ^{37}K ($T_{1/2} = 1.22$ s), ^{39}Ca ($T_{1/2} = 860$ ms) and ^{38}Ca ($T_{1/2} = 439$ ms). The production of these short-lived nuclides is investigated with a 5 s on/5 s off beam pulsing. The MCS spectrum of the 511 keV intensity versus time during the beam-off period is shown in figure 6, right. As ^{38}Ca has a half-life that is 2–3 times shorter than those of the other short-lived nuclides to be considered, a substantial production would be visible at the beginning of the spectrum. Such evidence is not seen leading to the conclusion that ^{38}Ca is not produced in relevant quantities. This is supported by the absence in the gamma ray spectrum of the relatively low energy (1568 keV) and high branching ratio (20%) gamma ray emitted in the decay of ^{38}Ca . The other three short

half-lives are close together and thus require special care in disentangling. Unfortunately, the gamma ray spectra are of no help in this matter: $^{38\text{m}}\text{K}$ and ^{39}Ca do not emit gamma rays whereas the most intense ^{37}K gamma ray has a high energy (2796 keV) and small branching ratio (2.04%). A fit of the time spectrum with the $^{38\text{g}}\text{K}$ decay and one of the short-lived nuclides shows the best fit for $^{38\text{m}}\text{K}$ (reduced $\chi^2 = 3.84$). However, the rather poor reduced χ^2 points to the presence of another short-lived nuclide. A fit with the $^{38\text{g}}\text{K}$ decay and a decay with the half-life as free fit parameter gives a fitted half-life of 976 ms, indicating that, next to $^{38\text{m}}\text{K}$, a longer-lived nuclide is present. This points to a contribution of ^{37}K . A fit with the decays of $^{38\text{g}}\text{K}$, $^{38\text{m}}\text{K}$ and ^{37}K results in a much improved reduced χ^2 of 2.15. We conclude that next to the well-known nuclide $^{38\text{g}}\text{K}$, both $^{38\text{m}}\text{K}$ and ^{37}K are produced in relevant quantities. No evidence of the production of ^{38}Ca and ^{39}Ca is seen.

Disentangling the contributions of the short-lived nuclides with absolute certainty requires a more sophisticated experiment. This is beyond the scope of this work. However, to determine the usefulness in proton therapy, only the production rate and approximate half-life are relevant, not the exact nature of the nuclides, and these are determined with sufficient accuracy in the present work.

Figure 6, right, shows the combined data of two separate irradiations. A separate analysis of these irradiations yields $^{38\text{g}}\text{K}$ productions of $5.74 \pm 0.06 \times 10^{-4}$ and $5.58 \pm 0.05 \times 10^{-4}$ per proton. The closeness of these values (ratio = 1.029 ± 0.014) shows the good reproducibility of the measurements within one experiment.

3.1.8. Correction for escaping positrons. Positrons escaping the target do not annihilate in the target and thus do not contribute to the number of detected 511 keV photons. The fraction of escaping positrons was determined by Monte Carlo simulation using the GATE simulation toolkit (Jan *et al* 2011). The fraction depends on the production profile in the target, and thus the cross section versus proton energy, which is not known experimentally for the short-lived PET nuclides. As an approximation, we assumed a constant cross section from the entrance of the target (proton energy 55 MeV) up to a depth where the proton energy equals the reaction threshold. The reaction threshold was estimated from experimental data (EXFOR 2015) of the same reaction channels on target nuclides close to the ones used here. For the production of ^9C on carbon, the fraction of escaping positrons was estimated based on the simulations for ^{12}N and ^8B which have a comparable positron end-point energy. This is sufficiently accurate as only an upper limit of the production of ^9C was established. The spatial profile of the proton beam used in the experiment was modeled as a 2D Gaussian with FWHM = 7 mm, a value determined from the Gafchromic images taken during the experiments. The positron energy spectrum was calculated using equation (9.25) from Krane (1988) using the known positron end-point energies. Concerning the long-lived nuclides: for the production of ^{15}O on water and ^{10}C on carbon, a production profile based on the experimental cross sections is used. For the production of ^{14}O on water, no experimental cross section data is available. We used the same production profile as that of ^{10}C on carbon, adjusted to the different target material, because both represent the same reaction channel. Table 3 gives the positron end-point energy and branching ratio for the main decay branches as well as the fraction of escaping positrons resulting from the simulations. The relative systematic uncertainty on the fraction of escaping positrons is estimated to be 10%.

The measured nuclide productions corrected for the fraction of escaping positrons are given in table 4. For the nuclides ^9C and ^{30}S , which have two significant positron decay branches, an average correction factor taking the relative branching ratios into account is applied. For the other nuclides, the correction factor for the main decay branch is used as this branch represents close to 100% of all decays.

Table 3. Fraction of positrons escaping from the target for the main positron emission branches.

Nuclide	Target	Positron end-point energy (MeV)	Positron emission branching ratio (%)	Fraction of escaping positrons (%)
¹⁵ O	Water	1.732	99.9	3.4
¹⁴ O	Water	1.808	99.3	5.9
¹² N	Carbon	16.316	94.6	53
¹¹ C	Carbon	0.960	99.8	1.3
¹⁰ C	Carbon	1.908	98.5	7.4
⁹ C	Carbon	15.476 ^a	47 ^a	50 ^c
		13.136 ^a	35 ^a	
⁸ B	Carbon	14.1 ^b	>88 ^b	46
³⁰ P	Phosphorus	3.210	99.8	14
²⁹ P	Phosphorus	3.921	98.2	23
³⁰ S	Phosphorus	4.439	76.1	29
		5.116	21.3	36
^{38g} K	Calcium	2.724	99.3	12
^{38m} K	Calcium	5.022	99.9	43
³⁷ K	Calcium	5.125	97.8	44

^a Gete (2000).^b Ajzenberg-Selove (1988).^c Estimate based on the simulation for ⁸B, see text.*Note:* The positron end-point energies and branching ratios are from NNDC (2015) unless otherwise noted.

3.2. Production of PET nuclides in tissue materials and PMMA

In this section, the production rates measured using targets of simple composition (water, carbon, phosphorus and calcium) are used to determine the production in some representative tissue materials and PMMA. The former allows to gauge the production of short-lived nuclides in patient irradiations, the latter is relevant as PMMA is an often used target material in investigations in this field.

The number of nuclei produced per incoming projectile is equal to the reaction cross section σ multiplied with the number of target nuclei per cm² N that is encountered by the projectile. Consider a target material with mass density ρ containing different elements with mass numbers A_i and weight fractions w_i . A projectile beam losing an energy ΔE over a target thickness Δd will encounter a number of target nuclei A_i per cm² equal to $N = \frac{w_i \rho}{A_i u} \Delta d = \frac{w_i}{A_i u} \frac{\Delta E}{dE/d(\rho x)}$, with u the atomic mass unit and $dE/d(\rho x)$ the mass stopping power of the projectile in the target material. This formula is valid if the stopping power can be considered constant over the energy loss ΔE .

Relevant in this work is the production in different materials over an equal proton energy loss, namely the full stopping of 55 MeV protons. Considering production of a nuclide via the same nuclear reaction over the same energy loss in two materials, the production ratio is given by:

$$\frac{P_1}{P_2} = \frac{w_1 (dE/d(\rho x))_2}{w_2 (dE/d(\rho x))_1} \quad (4)$$

Over the energy range of interest here (below 55 MeV), the proton stopping power ratios of the materials considered are constant to better than a few percent. One can thus use equation (4) over the full stopping of 55 MeV protons.

Table 4. Production of positron emitting nuclides per 55 MeV proton stopped in the target, with the statistical uncertainty from the fits of the time spectra.

Nuclide	Target	Experiment number	Production per proton ($\pm$ statistical uncertainty)	Systematic uncertainty (%)
^{15}O	Water	1	$8.83 \pm 0.11 \times 10^{-3}$	3
^{14}O	Water	2	$7.3 \pm 0.5 \times 10^{-5}$	20
^{12}N , ^{13}O combined	Water	1	$<7 \times 10^{-5}$	12
^{11}C	Carbon	1	$8.04 \pm 0.10 \times 10^{-3}$	3
^{10}C	Carbon	1	$3.08 \pm 0.08 \times 10^{-4}$	3
^9C	Carbon	1	$<5 \times 10^{-4}$	10
^{12}N	Carbon	1	$7.32 \pm 0.16 \times 10^{-4}$	12
^8B	Carbon	1	$1.1 \pm 0.3 \times 10^{-5}$	9
^{29}P	Phosphorus	2	$1.11 \pm 0.02 \times 10^{-3}$	4
^{30}P	Phosphorus	2	$5.44 \pm 0.03 \times 10^{-3}$	3
^{30}S	Phosphorus	2	$1.3 \pm 0.2 \times 10^{-4}$	5
$^{38\text{g}}\text{K}$	Calcium	2	$5.74 \pm 0.06 \times 10^{-4}$	3
			$5.58 \pm 0.05 \times 10^{-4}$	3
$^{38\text{m}}\text{K}$	Calcium	2	$6.38 \pm 0.17 \times 10^{-4}$	8
^{37}K	Calcium	2	$1.6 \pm 0.2 \times 10^{-4}$	8

Note: The combined systematic uncertainty due to the efficiency calibration of the germanium detector and the determination of the fraction of positrons escaping from the target is given separately.

Next to PMMA, we calculate the production of short-lived nuclides in a number of tissue materials: carbon-rich (adipose) and oxygen-rich (skeletal muscle) soft tissue, and compact and cortical bone. Table 5 gives the relevant material properties and the number of nuclei produced per 55 MeV proton stopped in the materials. In the cases where two experimental values were measured (for ^{15}O and $^{38\text{g}}\text{K}$, see table 4) the average value is used. The production of nuclides for which only an upper limit was determined ($^{12}\text{N}/^{13}\text{O}$ produced on oxygen and ^9C produced on carbon, see table 4) has not been calculated. Statistical and systematic uncertainties on these numbers can be transported from table 4. Values are shown with 2 or 3 significant digits depending on the size of the uncertainty.

3.3. Number of beam-on PET decays

The usefulness of a positron emitter for *in vivo* dose delivery verification depends, amongst other factors, on the number of counts it generates in the PET scanner used, and thus the number of decays during the PET acquisition. This number depends on the PET acquisition time structure with respect to the irradiation time structure and the radioactive half-life of the nuclide. Biological washout, which depends on the chemical nature of the nuclide and the properties of the tissue in which it is produced, is not considered in this first order calculation.

In the following, we assume a continuous (as compared to the relevant decay half-lives) proton beam, as e.g. delivered by a cyclotron, the most commonly used accelerator type in proton therapy. Figures 7 and 8 show the number of decays of PET nuclides integrated from the start of an irradiation as function of time in the irradiation, for an irradiation with 55 MeV protons and scaled to a beam intensity of 1 proton per second, for the materials being

Table 5. Number of nuclei produced per 55 MeV proton stopped in tissue materials and PMMA.

Material	ICRP adipose tissue	ICRP skeletal muscle	ICRU compact bone	ICRP cortical bone	PMMA
Density (g cm^{-3})	0.92	1.04	1.85	1.85	1.19
Weight fractions (%)	C: 63.7, O: 23.2	C: 10.8, O: 75.5	C: 27.8, O: 41.0, P: 7.0, Ca: 14.7	C: 14.4, O: 44.6, P: 10.5, Ca: 21.0	C: 60.0, O: 32.0
Range 55 MeV protons (g cm^{-2})	2.56	2.67	2.85	2.97	2.71
Product nuclide (target)					
^{15}O (oxygen)	2.24×10^{-3}	7.58×10^{-3}	4.39×10^{-3}	4.96×10^{-3}	3.26×10^{-3}
^{14}O (oxygen)	1.8×10^{-5}	6.3×10^{-5}	3.6×10^{-5}	4.1×10^{-5}	2.7×10^{-5}
^{11}C (carbon)	4.42×10^{-3}	7.81×10^{-4}	2.14×10^{-3}	1.15×10^{-3}	4.41×10^{-3}
^{10}C (carbon)	1.69×10^{-4}	2.99×10^{-5}	8.21×10^{-5}	4.42×10^{-5}	1.69×10^{-4}
^{12}N (carbon)	4.0×10^{-4}	7.1×10^{-5}	2.0×10^{-4}	1.1×10^{-4}	4.0×10^{-4}
^8B (carbon)	6.3×10^{-6}	1.1×10^{-6}	3.0×10^{-6}	1.6×10^{-6}	6.3×10^{-6}
^{29}P (phosphorus)			6.5×10^{-5}	1.0×10^{-4}	
^{30}P (phosphorus)			3.17×10^{-4}	4.94×10^{-4}	
^{30}S (phosphorus)			7.7×10^{-6}	1.2×10^{-5}	
^{38g}K (calcium)			6.28×10^{-5}	9.33×10^{-5}	
^{38m}K (calcium)			7.1×10^{-5}	1.1×10^{-4}	
^{37}K (calcium)			1.8×10^{-5}	2.7×10^{-5}	

Note: The materials, their density, the weight fractions of the relevant constituent elements and the range of 55 MeV protons are given in the top row.

Figure 7. The number of decays of PET nuclides integrated from the start of an irradiation as function of time during the irradiation, for an irradiation with 55 MeV protons and scaled to a beam intensity of 1 proton per second, for adipose, skeletal muscle, and PMMA. Short-lived nuclides are shown with solid lines, long-lived ones with dashed lines. The right column zooms in on the first second of the irradiation.

considered in section 3.2. Only the most abundant short-lived nuclides are shown: ¹²N on carbon, ²⁹P on phosphorus and ^{38m}K on calcium, together with the most abundantly produced long-lived nuclides: ¹⁵O on oxygen, ¹¹C on carbon, ³⁰P on phosphorus and ^{38g}K on calcium. The production of ¹¹C on oxygen is not included because of the much lower reaction cross section below 55 MeV as compared to the production on carbon. In order to better see the number of decays on very short time scales and thus judge the potential for prompt information, the right column of figures 7 and 8 zooms in on the first second of the irradiation.

3.4. Image blurring due to the large positron energies

In the decay of a positron emitting nucleus, positrons are emitted isotropically with an energy ranging from zero to the endpoint energy. The resulting positron range distribution causes spatial blurring of the PET images. For the relatively long-lived nuclides used in nuclear medicine

Figure 8. The number of decays of PET nuclides integrated from the start of an irradiation as function of time in the irradiation, for an irradiation with 55 MeV protons and scaled to a beam intensity of 1 proton per second, for compact bone and cortical bone. Short-lived nuclides are shown with solid lines, long-lived ones with dashed lines. The right column zooms in on the first second of the irradiation. The lines in the right column figures represent, from top to bottom, the contributions from ^{12}N , $^{38\text{m}}\text{K}$, ^{15}O , ^{29}P , ^{30}P , ^{11}C and $^{38\text{g}}\text{K}$.

(half-lives longer than that of ^{15}O , 2 min), this blurring is negligible in comparison to the other factors contributing to image spatial resolution. As the positron endpoint energy typically increases with decreasing half-life, we have considered positron range blurring for the short-lived positron emitting nuclides observed in this work. A procedure identical to Levin and Hoffman (1999) was followed. GEANT4-based (Agostinelli 2003) Monte Carlo simulations of point sources in water were performed using the same positron energy distributions as used in the simulation of positron escape from the targets (see section 3.1.8). As discussed by Levin and Hoffman (1999), the 1D range distribution is the relevant one for a tomographic imaging modality as PET. Our simulation for ^{15}O agrees very well with the distribution obtained by Levin and Hoffman (1999).

The 1D range distributions show a sharp central peak and long tails and can therefore not very adequately be described by their full-width-at-half-maximum (FWHM) and full-width-at-tenth-maximum (FWTM) values. A better measure is the root-mean-square (rms) of the distributions, as e.g. used by Derenzo (1986). Figure 9 shows the rms of the 1D positron range distribution in water as function of the positron endpoint energy. The following nuclides, in

Figure 9. Root-mean-square of the 1D positron range distributions in water as function of the positron endpoint energy. See text for details.

order of increasing endpoint energy, are included in the figure: ^{15}O , ^{14}O , $^{38\text{g}}\text{K}$, ^{30}P , ^{29}P , ^{30}S (4.4 MeV endpoint energy decay branch), $^{38\text{m}}\text{K}$, ^{30}S (5.1 MeV endpoint energy decay branch), ^{37}K , ^8B , ^{12}N . A very linear behaviour is observed. Note that it is known that for positron endpoint energies below the smallest shown in figure 9, the rms curve deviates from this linear behaviour (Derenzo 1986).

The rms range for ^{12}N is 18 mm, so beam-on PET of carbon-rich tissue will suffer image blurring due to the observation of ^{12}N . The size of this effect will depend on the ratio of ^{12}N to long-lived nuclides detected by the PET system and thus on factors such as tissue composition and duration of the irradiation. The short-lived nuclides produced on calcium and phosphorus in bone tissue have rms ranges between 3.6 and 5.0 mm in water. Taking into account that the positron range is shorter in dense bone tissue, PET image blurring when imaging these nuclides will be limited, making these nuclides useful for *in vivo* dose delivery verification.

4. Discussion

4.1. Re-interpretation of earlier observation of short-lived nuclides produced on bone

Miyatake *et al* (2010) measured the decay curves of positron emitter activity after proton irradiation. For head-and-neck and prostate tumour cases, they observe fast decay components with half-lives of 2.6 ± 1.5 s and 1.5 ± 0.4 s, respectively (the uncertainties on the half-life values reflect the variation across the five patients investigated). These observations were interpreted by the production of ^{38}Ca ($T_{1/2} = 439$ ms) and ^{39}Ca ($T_{1/2} = 860$ ms) on calcium, considering that a lot of bone tissue is irradiated in these cases. Note that the production of radionuclides on phosphorus was not considered. At the end of irradiation, 20–40% of the total positron emitter activity originated from these short-lived nuclides. The interpretation by Miyatake *et al* (2010) of the short-lived nuclides observed disagrees with our non-observation of the production of ^{38}Ca and ^{39}Ca on calcium. The most abundantly produced short-lived nuclides on calcium and phosphorus we observe are $^{38\text{m}}\text{K}$ and ^{29}P respectively. The respective half-lives, 924 ms and 4.14 s are compatible with the half-lives observed by Miyatake *et al* (2010). We therefore conclude that in all likelihood, Miyatake *et al* (2010) have observed the production of a combination of $^{38\text{m}}\text{K}$ and ^{29}P and not ^{38}Ca and ^{39}Ca . This conclusion is supported by the well-known production of long-lived $^{38\text{g}}\text{K}$, i.e. the ^{38}K nuclear ground state, on calcium and general properties of nuclear reaction cross sections. The spin-parity of the

target nucleus ^{40}Ca , 0^+ , better matches the spin-parity of $^{38\text{m}}\text{K}$, 0^+ , than the spin-parity of $^{38\text{g}}\text{K}$, 3^+ . Combined with the low excitation energy of $^{38\text{m}}\text{K}$ (130 keV) it is quite impossible to produce $^{38\text{g}}\text{K}$ in substantial quantities without $^{38\text{m}}\text{K}$ being produced as well. Our observation of about equal production of both is compatible with these general nuclear structure considerations.

4.2. Beam-on PET decays

In carbon-rich, oxygen-poor materials, the number of PET decays from ^{12}N dominates for irradiation times up to 70 s in adipose tissue and 45 s in PMMA. For an irradiation to deliver a dose of 2 Gy in a volume of 1 liter, which typically takes 70 s, the fraction of ^{12}N decays relative to the total is 41% in adipose and 34% in PMMA. This indicates that in beam-on PET during proton irradiations, the PET image in carbon-rich tissue will be deteriorated due to ^{12}N positron range blurring (see section 3.4). In oxygen-rich tissue such as illustrated by skeletal muscle here, the deterioration due to ^{12}N will obviously be less severe: for an irradiation time of 70 s, the ^{12}N decays represent just 5% of the total.

For the two types of bone considered, ^{15}O delivers the dominant contribution to beam-on PET except for irradiation times below about 15 s in compact bone and about 8 s in cortical bone; for shorter irradiation times, ^{12}N decays dominate. The short-lived nuclides produced on phosphorus and calcium, ^{29}P and $^{38\text{m}}\text{K}$, provide a significant increase in PET decays compared to the long-lived nuclides ^{30}P and $^{38\text{g}}\text{K}$. As the production of $^{38\text{m}}\text{K}$ is slightly higher than that of $^{38\text{g}}\text{K}$, $^{38\text{m}}\text{K}$ will always dominate over $^{38\text{g}}\text{K}$ in beam-on PET. For an irradiation time of 70 s for example, $^{38\text{m}}\text{K}$ provides 22 times more decays, and thus PET image counts, than $^{38\text{g}}\text{K}$. The observation of ^{29}P in addition to ^{30}P is not as advantageous because the production of ^{29}P is 5 times smaller than that of ^{30}P . Considering nuclides created on phosphorus and calcium, the short-lived ones provide, during a 70 s irradiation, 2.5 times more decays than the long-lived ones. Bone tissue will thus be better visible in beam-on PET compared to PET imaging after an irradiation.

4.3. The potential of ^{12}N for prompt PET imaging

The experimental production rates of short-lived positron emitters (as defined in this work, i.e. $T_{1/2} < 19$ s) allow an estimate of the potential to obtain *in vivo* dose delivery information with PET on a time scale significantly shorter than the duration of an irradiation. In the following, we first concentrate on ^{12}N : as it is produced on carbon which is abundant throughout the body, it is the most generally useful short-lived isotope. Furthermore, its very short half-life of 11 ms may allow a response at a time scale of 50–100 ms.

Both PET and prompt gamma imaging for *in vivo* dose delivery verification are challenged by poor counting statistics; the quality of the information obtained depends substantially on the number of counts detected. We therefore compare the potential of ^{12}N PET imaging with prompt gamma imaging at the level of the number of counts.

We consider the knife-edge slit camera developed by Smeets *et al* (2012) and Perali *et al* (2014) to be the most advanced prompt gamma imaging system presently available. The camera measures 1D prompt gamma profiles, which, together with knowledge of the transverse position of the beam, allow 3D imaging of the proton range. In order to remove statistical noise and correct for efficiency non-uniformity of the detectors, Perali *et al* (2014) apply a 20 mm Gaussian smoothing to the measured profiles. This smoothing does not result in the loss of information as the collimator used has an effective geometric resolution of 22 mm. For pencil beam irradiations of a PMMA target with resp. 100, 160 and 230 MeV protons,

a 2σ -precision of 4 mm for the measurement of a target shift is obtained for resp. 0.5×10^8 , 1.4×10^8 and 3.4×10^8 protons. From figures 11 and 12 from Perali *et al* (2014), taking into account the slit resolution, we estimate that the final 55 MeV (2.3 cm) of the proton range yields 3×10^{-6} counts per proton.

The production of ^{12}N in PMMA is 4.0×10^{-4} per 55 MeV proton, see table 5. Integrated over a time scale of several times the half-life, there will thus be 4.0×10^{-4} ^{12}N decays per proton. In order not to hinder the proton beam, a limited-angle PET scanner is most often considered for *in situ*, and thus also beam-on, use. Crespo *et al* (2006) investigate the coincidence detection efficiency of partial-ring *in situ* PET scanners as function of several parameters. The scanners considered have a diameter of 41.2 or 45.8 cm and use 20 mm thick LSO scintillation crystals. Crespo *et al* (2006) calculate that a scanner that (1) focuses on the relatively small region of the distal edge of an irradiation, (2) has an angular coverage of 1/2, and (3) has an axial length of 22 cm, has a coincidence detection efficiency of about 6%. Using this value, we arrive at 2.4×10^{-5} ^{12}N coincidence counts per proton.

Image blurring due to large positron endpoint energies (see section 3.4), not present in prompt gamma imaging, needs to be considered when comparing ^{12}N PET with prompt gamma imaging. The 1D projection of the ^{12}N positron range distribution has an rms of 18 mm (see section 3.4), much larger than the typical PET scanner spatial resolution (about 5 mm). Even though the positron range distribution is sharper than a Gaussian (Levin and Hoffman 1999), for the purpose of the present consideration, we can state that the effect of the ^{12}N positron range distribution on the PET image is comparable to that of the 22 mm slit resolution in the prompt gamma imaging by Perali *et al* (2014). We thus finally conclude that, for PMMA, the number of PET counts from ^{12}N is about 10 times larger than the number of prompt gamma counts in the prompt gamma imaging system that is presently closest to clinical implementation and this for similar image spatial resolution. ^{12}N PET may thus be expected to provide superior proton range information.

When considering irradiations in human tissue, the ratio of ^{12}N PET to prompt gamma counts depends on the carbon content of the tissue because ^{12}N is only produced in useful quantities on carbon whereas prompt gamma ray production is rather independent on carbon-to-oxygen ratio (see e.g. Polf *et al* 2009a), with the sum of carbon and oxygen fractions being more or less the same for all tissues. For adipose, with a carbon-to-oxygen ratio of about 2, the ratio of ^{12}N PET to prompt gamma counts will be similar to that of PMMA, i.e. about 10. For other tissues, carbon-to-oxygen ratios lie mostly between 1/1.5 and 1/6 (Woodard and White 1986) and the ratio of ^{12}N PET to prompt gamma counts will be from about 3 to 1. Based on number of counts, ^{12}N PET imaging will thus for any tissue provide proton range information equal or superior to that obtained in prompt gamma imaging using a knife-edge slit camera.

Finally we discuss some important aspects of the development of a practical implementation of prompt ^{12}N PET imaging. Basic detector issues such as count rate capability and radiation hardness (especially of SiPM-type photosensors) are common to beam-on PET and prompt gamma imaging systems based on scintillation crystals (such as the knife-edge slit camera discussed above). Modern PET detectors have been shown to be capable of beam-on PET data acquisition, see e.g. Shao *et al* (2014). Interference from neutron-induced signals is expected to be less compared to prompt gamma imaging because of the coincidence detection requirement in PET, and, in comparison with a collimator-based prompt gamma camera, the absence of a thick heavy-element collimator. A main challenge is to develop specific image reconstruction methods. For information on the progress of an irradiation to be available as quickly as possible (i.e. at a time scale of a few times the radioactive half-life, so a time scale of about 50 ms for ^{12}N), image information needs to be generated at the same time scale. This prohibits the use of standard PET image reconstruction techniques. One needs a ‘direct’ reconstruction method in

which an image is updated in real-time as the PET data acquisition is in progress. An example of this is direct time-of-flight image reconstruction whose feasibility for real-time beam-on PET was studied by Crespo *et al* (2007). As an irradiation progresses, the contribution of the longer-lived ^{15}O to the PET image will become more and more important (see figures 7 and 8). A way needs to be found to subtract the slowly varying ^{15}O contribution from the image. Data taken during no-beam periods in-between energy planes could be used for this. In conclusion, the technical implementation of ^{12}N beam-on PET is feasible and future work will need to focus on real-time image reconstruction and its coupling to the beam delivery time structure, and on the separation of the ^{12}N -related image contribution from that of longer-lived isotopes.

5. Conclusions

As very little is known on the production of short-lived positron emitting nuclides (defined for the purpose of this work to be nuclides with $T_{1/2} < 19$ s) in proton therapy, we determined which ones are relevant for *in vivo* dose delivery verification of proton therapy by measuring the production of short-lived positron emitters in the stopping of 55 MeV protons in water, carbon, phosphorus and calcium. The most copiously produced short-lived nuclides and their production rates relative to the relevant long-lived nuclides are: ^{12}N ($T_{1/2} = 11$ ms) on carbon (9% of the ^{11}C production), ^{29}P ($T_{1/2} = 4.1$ s) on phosphorus (20% of the ^{30}P production) and $^{38\text{m}}\text{K}$ ($T_{1/2} = 0.92$ s) on calcium (113% of the $^{38\text{g}}\text{K}$ production). No short-lived nuclides are produced on oxygen. Using the experimental results, the number of decays of PET nuclides integrated from the start of an irradiation as function of time during the irradiation is calculated for PMMA, adipose, skeletal muscle and compact and cortical bone. The most noticeable result is that for an irradiation in (carbon-rich) adipose tissue, ^{12}N will dominate the beam-on PET image up to 70 s. On bone tissue, ^{12}N dominates over ^{15}O during the first 8–15 s (depending on the carbon-to-oxygen ratio). Considering nuclides created on phosphorus and calcium, the short-lived ones provide 2.5 times more beam-on PET counts than the long-lived ones during a 70 s irradiation. Bone tissue will thus be better visible in beam-on PET compared to PET imaging after an irradiation. Information on the energy-dependent production of ^{12}N , ^{29}P and $^{38\text{m}}\text{K}$ is needed in order to study in more detail the effect of these nuclides on the quality of *in vivo* treatment verification in proton therapy with PET imaging.

The ^{12}N positron range image blurring (rms of 18 mm) is similar to the slit resolution (22 mm) of the optimized knife-edge slit camera discussed by Perali *et al* (2014), the prompt gamma imaging device that is closest to being tested in patient irradiations. From the estimated number of ^{12}N PET counts, we conclude that, for any tissue, ^{12}N PET imaging has the potential to provide equal or superior proton range information compared to prompt gamma imaging with an optimized knife-edge slit camera. As the main challenges towards the practical implementation of ^{12}N PET imaging, we see the development of real-time image reconstruction and its coupling to the beam delivery time structure and the separation of the ^{12}N -related image contribution from that of longer-lived isotopes.

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