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First results of the INSIDE in-beam PET scanner for the on-line monitoring of particle therapy treatments

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Abstract: Quality assessment of particle therapy treatments by means of PET systems has been carried out since late '90 and it is one of the most promising in-vivo non invasive monitoring techniques employed clinically. It can be performed with a diagnostic PET scanners installed outside the treatment room (off-line monitoring) or inside the treatment room (in-room monitoring). However the most efficient way is by integrating a PET scanner with the treatment delivery system (on-line monitoring) so that the biological wash out and the patient repositioning errors are minimized. In this work we present the performance of the in-beam PET scanner developed within the INSIDE project. The INSIDE PET scanner is made of two planar heads, 10 cm wide (transaxially)× 25 cm long (axially), composed of pixellated LFS crystals coupled to Hamamatsu MPPCs. Custom designed Front-End Electronics (FE) and Data AcQuisition (DAQ) systems allow an on-line reconstruction of PET images from separated in-spill and inter-spill data sets. The INSIDE PET scanner has been recently delivered at the CNAO (Pavia, Italy) hadrontherapy facility and the first experimental measurements have been carried out. Homogeneous PMMA phantoms and PMMA phantoms with small air and bone inserts were irradiated with monoenergetic clinical proton beams. The activity range was evaluated at various benchmark positions within the field of view to assess the homogeneity of response of the PET system. Repeated irradiations of PMMA phantoms with clinical spread out Bragg peak proton beams were performed to evaluate the reproducibility of the PET signal. The results found in this work show that the response of the INSIDE PET scanner is independent of the position within the radiation field. The results also show the capability of the INSIDE PET scanner to distinguish variations of the activity range due to small tissue inhomogeneities. Finally, the reproducibility of the activity range measurement was within 1 mm.

Keywords: Instrumentation for hadron therapy; PET

Contents

1 Introduction

Particle therapy is a special kind of radiotherapy which makes use of heavy charged particle beams instead of the conventional photon beams. One of the advantages of using heavy charged particle beams is the possibility to deliver a dose distribution more conformal with the tumor volume thanks to the finite range of the particle beam and the sharp ionization peak at the end of the particle range, the Bragg Peak.

However this advantage cannot be fully exploited due to various sources of uncertainty like artifacts in the planning CT, for example, or by uncertainties in the conversion of the Hounsfield Units to stopping powers, or by temporary anatomical/physiological changes of the patient. These uncertainties can cause overdosage of healthy tissues and underdosage of the tumor volume. Uncertainties in the delivery of the treatment are taken into account in the clinical procedures by introducing large safety margins (for example 3% uncertainty in the dose delivered and 3 mm uncertainty in the delivery point for proton therapy). As a consequence, the full potential of particle therapy treatments is not exploited. To increase the reliability of the delivered treatment an on-line monitoring of the particle range would be desirable [1].

A well established, non-invasive in-vivo monitoring technique is the Positron Emission Tomography (PET) [2, 3]. PET scanners are used to measure the spatial distribution of the β^+ emitters created during the irradiation, as for example ^{11}C, ^{15}O or ^{10}C, among the most abundant. Dose and β^+ emitters activity distribution depend on ion species, energy and tissue composition in a different

way. However from the activity distribution it is possible to infer changes in the beam particle range, which is a crucial parameter for the quality assurance of the treatments [4–6].

PET monitoring is tipically performed with a clinical PET scanner installed inside the treatment room (in-room PET monitoring) or outside the treatment room (off-line monitoring). However, PET scanners integrated in the treatment gantry, or nozzle, and operated during the dose delivery (on-line or in-beam monitoring) allows achieving higher sensitivities in the measurement of the low activity levels induced by the beam [7]. In fact, during the irradiation the activity signal builds up and reaches its maximum at the end of the beam delivery, also the one arising from the nuclides with a short half life like ^{10}C or ^{12}N. Furthermore, the biological washout is minimized and patient repositioning errors are avoided.

Recently an on-line monitoring system has been developed within the INSIDE (INnovative SolutIons for DosimEtry in hadrontherapy) project. The INSIDE project was born from the collaboration of 4 italian universities (University of Pisa, University of Torino, University of Roma "La Sapienza" and Polytechnical University of Bari) and the Italian Institute of Nuclear Physics (INFN). The aim of the project was to build a fast in-beam monitoring system for the head and neck particle therapy treatments delivered at the CNAO (Centro Nazionale di Adroterapia Oncologica) hadrontherapy facility in Pavia, Italy. The INSIDE monitoring system is a bi-modal monitoring system because it is made of a particle tracker (also called dose profiler) and a dual-head PET scanner. The particle tracker recontructs the beam particles track inside the patient from the prompt charged particles emitted during ion irradiation, while the PET scanner measures the spatial distribution of the β^+ emitter isotopes [8, 9].

The INSIDE PET scanner has been lately installed at the CNAO hadrontherapy centre in Pavia, Italy. The first PET images of PMMA phantoms irradiated with proton beams have been successfully reconstructed and compared with the Monte Carlo simulations [10].

In this work we present the capabilities of proton beam range monitoring of the INSIDE PET scanner in terms of homogeneity within the field of view and reproducibility of the measurement of the length of the β^+ activity depth profile (the activity range). PMMA phantoms both homogeneous and with inserts of different materials were irradiated with monoenergetic and Spread Out Bragg Peak (SOBP) proton beams. The activity range was evaluated at various benchmark points within the field of view.

2 Methods and Materials

2.1 The PET scanner

The INSIDE PET scanner is composed of two opposite planar heads. Each head is made of 10 detection modules arranged in a 2×5 array. The detection module is made of an array of 16×16 pixelated (3×3×20 mm^3) Lutetium Fine Silicate (LFS) scintillating crystals coupled one to one to a 16×16 Multi Pixel Photon Counters (MPPC, produced by the Hamamatsu Photonics, Japan) array. The detection module is read-out by 4 TOFPET ASICs [11] which give information on the energy released in each channel and the detection time of each event.

A data processing system based on FPGAs selects the 511 keV events which are then analyzed on-line in a data acquisition server (32 Hyper Thread cores and 128 GB RAM) to find and store the coincidence data.

An iterative algorithm based on the Maximum Likelihood Expectation Maximization method is used to reconstruct the PET images. Details about the reconstruction algorithm can be found in [12]. The reconstructed Field Of View (FOV) is 224×112×264 mm^3 with a voxel size of 1.6×1.6×1.6 mm^3.

2.2 Experimental measurements

The INSIDE PET system was installed in a treatment room of the CNAO.

During the irradiations the PET scanner was positioned so that the centre of the FOV was at the beam isocentre. The distance between the two PET heads was set to 50 cm, which is the distance that will be set for the clinical usage.

A schematic picture (not to scale) of the experimental set-up is shown in figure 1 (a).

The experimental measurements focused on the evaluation of:

1. the homogeneity of response within the FOV
2. the capability of detecting tissue inhomogeneities
3. the reproducibility of the PET signal

2.2.1 Homogeneity of response

The homogeneity of response of the PET system was tested by irradiating an homogeneous PMMA phantom ($10 \times 10 \times 20$ cm^3) with a monoenergetic proton beam (144.4 MeV) scanning a 9×9 cm^2 area in the x-y plane (see figure 1 (a) for axis reference). The irradiation was performed starting from bottom to the top, in a 32×32 matrix of beam spots. The distance between two adjacent spots was 3 mm. About 10^{11} protons were delivered. The irradiation lasted 26 minutes.

The PMMA phantom was positioned with the long side along the beam direction and it was centred at the isocentre.

The length of the activity depth profile was evaluated at various benchmark points. The position of the points is shown in figure 1 (b). The procedure for the evaluation of the length of the activity profile is described in section 2.3.

2.2.2 Response to different tissue composition

To test the capability of the PET system to distinguish different tissue compositions, a PMMA phantom with air and bone-equivalent inserts was made in-house. The phantom was $10 \times 10 \times 19.6$ cm^3. The air and bone inserts were 0.6 cm thick and they were placed at a depth of 5 cm. An illustration of the in-house phantom is shown in figure 2.

The irradiation of the phantom was carried out as described in sec. 2.2.1.

The length of the activity depth profile was evaluated at the same benchmark points for the evaluation of the homogeneity of response (see figure 1 (b)), with the exception of the points along the x and y axis to avoid the air-bone edges.

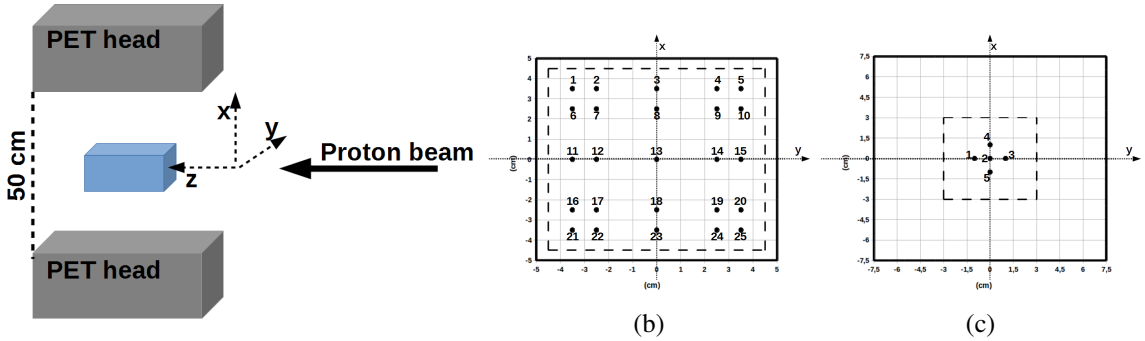

Figure 1: (a) Schematic picture of the experimental set up. The PET scanner was placed so that its field of view was centred at the beam isocentre. During the irradiations the PMMA phantoms were also centred at the beam isocentre. (b) Benchmark points for the evaluation of the homogeneity of response and the response to different tissue compositions. (c) Benchmark points for the evaluation of the reproducibility. In both figures (b) and (c), the outer square is the cross section of the PMMA phantom. The dashed line defines the irradiated area. Numbered points are the benchmark points where the length of the activity profile was calculated.

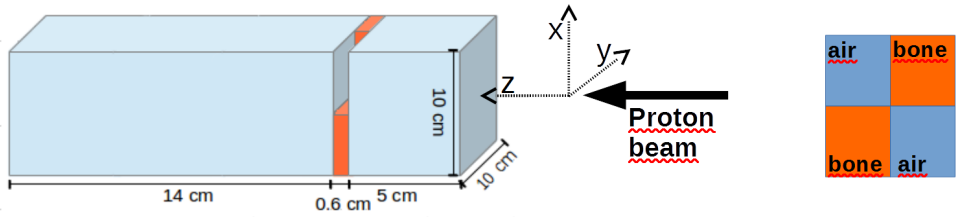

Figure 2: PMMA phantom with air and bone inserts made in-house for the assessment of the response to different tissue compositions. The inserts were arranged in a chessboard configuration.

2.2.3 Reproducibility

The reproducibility was evaluated by repeating three times the irradiation of an homogeneous PMMA phantom ($15 \times 15 \times 20$ cm^3) with a SOBP proton beam delivering a dose of 2 Gy in a 6×6×6 cm^3 volume. The PMMA phantom was centred at the beam isocentre and it was changed at each irradiation. Each irradiation lasted 3.5 minutes. The proton beam energy ranged from 129 MeV to 164 MeV.

The reproducibility was also tested by delivering to the PMMA phantoms a clinical treatment plan (1 Gy in the target volume). The plan delivery lasted 4 minutes and it was repeated twice. The proton beam energy ranged from 83 MeV to 150 MeV.

The length of the activity profile was evaluated at five benchmark points as shown in figure 1 (c). The procedure for the evaluation of the length of the activity profile is described in section 2.3.

2.3 Evaluation of the activity distal fall-off position

The CNAO hadrontherapy centre is a synchrotron based facility. The particle beam is characterized by spills (when the beam is actually delivered) lasting 1 s and 3 s of interspill pauses.

Although the PET data are acquired during the whole irradiation time, comprising both the spill and the interspill, in this work we focus on the PET images reconstructed using the data acquired during the interspill pauses only.

The 1-dimensional activity profile was measured by plotting the values of the voxels along the beam direction (z axis) of the reconstructed interspill images, averaged over 5×5 voxels in the x-y plane.

The rising edge and the falling edge of the activity profile were fitted separately with the function:

$$p = B + \frac{A - B}{1 + e^{s(z-d)}} \tag{2.1}$$

where B is the background, A is the maximum value, s is the fall-off slope and d is the inflection point.

The d value of the rising edge of the profile (d_{rising}) was chosen as an estimator of the position for the start of the activity profile, while the d value of the falling edge of the activity profile ($d_{falloff}$) was chosen as an estimator of the distal fall-off position. The error of the d parameter was the measurement error. The length of the activity profile was calculated as $d_{falloff} - d_{rising}$.

3 Results and discussion

3.1 Homogeneity of response

Figure 3 shows the length of the activity profile at various points within the radiation field after the irradiation of the homogeneous PMMA phantom. The standard deviation of the values is 0.3 mm with a maximum variation of 1 mm, which is comparable with the measurement error. We can conclude that the response of the PET system is homogeneous within 1 mm in the 9×9 cm^2 area centred in the FOV.

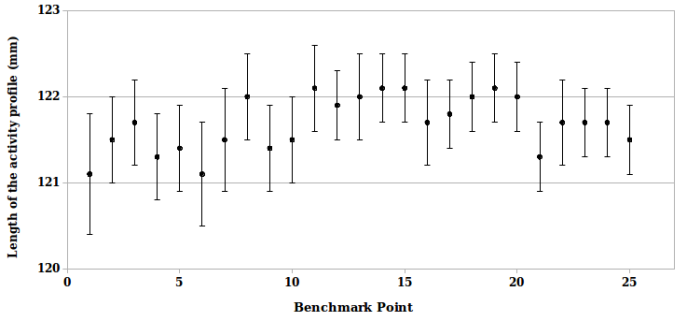

Figure 3: Length of the activity profile at the benchmark points after the irradiation of the homogeneous PMMA phantom with the 144 MeV proton beam.

3.2 Response to different tissue composition

Figure 4 shows the length of the activity profile at the benchmark points within the radiation field after the irradiation of the PMMA phantom with the air and bone inserts.

The higher values refer to the benchmark points corresponding to the air insert, while the lower values refer to the benchmark points corresponding to the bone insert.

The standard deviation of the activity legth of both groups is 0.3 mm. The maximum variation is below 1mm.

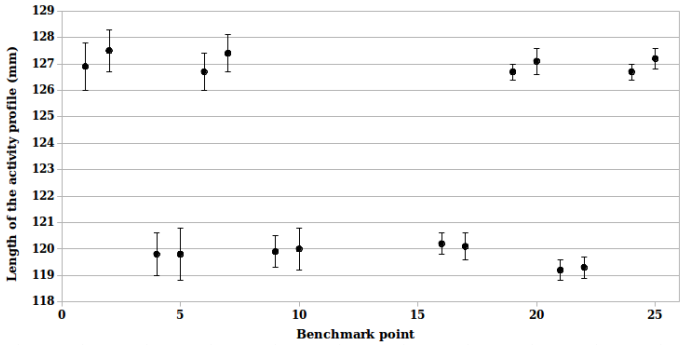

Figure 4: Length of the activity profile at the benchmark points after the irradiation of the PMMA phantom with the air (higher values) and bone (lower values) inserts.

3.3 Reproducibility

Table 1 summarizes the results of the reproducibility measurements. (a), (b) and (c) refer to the different irradiations while numbers refer to the benchmark points within the radiation field.

The standard deviation of the lengths of the activity profile at each benchmark point is comparable with the measurement error. We can therefore conclude that the reproducibility is within 1 mm in standard deviation.

Table 1: Length of the activity profile: Repeated irradiations ((a), (b) and (c)) of a 6×6×6 cm^3 volume and of two clinical treatment plans. Numbers in the table header refer to the benchmark points where the length of the activity profile was calculated.

Irradiation	Length of the activity profile (mm)				
	1	2	3	4	5
	6×6×6 cm^3 volume, Irradiation time= 3.5 min				
(a)	136±1	134±1	136±1	134±1	135±1
(b)	135±1	136±1	136±1	135±1	135±1
(c)	137±1	136±2	135±2	136±1	136±1
mean±SD	136±1	135±1	135.7±0.6	135±1	135.3±0.6
	Treatment plan 1, Irradiation time= 4 min				
(a)	84±1	76±1	71±1	77±1	74±1
(b)	83.6±0.8	75±1	72±1	76±1	73.2±0.9

4 Conclusions

In this work we have investigated the homogeneity of response and reproducibility of the INSIDE PET scanner during the irradiation of PMMA phantoms with clinical proton beams to assess the accuracy of the activity range verification.

The system response is uniform within the radiation field and differences in the activity range due to tissue inhomogeneities can be detected. The reproducibility of the PET signal in homogeneous PMMA phantoms was within 1 mm in irradiation conditions comparable to the clinical setting.

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References

[1] Knopf, A., Lomax, A., *In vivo proton range verification: a review*, *Physics in medicine and biology* **58.15** (2013).

[2] Parodi, K. *Vision 20/20: Positron emission tomography in radiation therapy planning, delivery, and monitoring*, *Medical physics* **42.12** (2015) 7153-7168.

[3] Del Guerra, A., Belcari,N., Bisogni, M. G., *Positron Emission Tomography: Its 65 years*, *RIVISTA DEL NUOVO CIMENTO* **39.4** (2016) 155-223.

[4] Fiedler, F., Shakirin, G., Skowron, J., Braess, H., Crespo, P., Kunath, D., Pawelke, J., Pönisch, F., Enghardt, W., *On the effectiveness of ion range determination from inbeam PET data*, *Phys. Med. Biol.* **55(7)** (2010).

[5] Parodi, K., F. Pönisch, Enghardt, W., *Experimental study on the feasibility of in-beam PET for accurate monitoring of proton therapy.*, *IEEE Trans. Nucl. Sci.* **52.3** (2005).

[6] Enghardt, W., Crespo, P., Fiedler, F., Hinz, R., Parodi, K., Pawelke, J., Pönisch, F. *Charged hadron tumour therapy monitoring by means of PET.*, *Nucl. Instrum. Meth. A* **525.1** (2004).

[7] Shakirin, G., Braess, H., Fiedler, F., Kunath, D., Laube, K., Parodi, K., Priegnitz, M., Enghardt, W. *Implementation and workflow for PET monitoring of therapeutic ion irradiation: a comparison of in-beam, in-room, and off-line techniques*, *Phys. Med. Biol.* **56.5** (2011).

[8] Marafini, M., et al. *The INSIDE Project: Innovative Solutions for In-Beam Dosimetry in Hadrontherapy*, *Acta Physica Polonica* **A. 127.5** (2015).

[9] Pennazio, F., et al. *A Study of Monitoring Performances with the INSIDE System*, *Acta Physica Polonica* **A. 127.5** (2015).

[10] Fiorina, E., and INSIDE Collaboration. *An integrated system for the online monitoring of particle therapy treatment accuracy*, *Nucl. Instrum. Meth. A* **824** (2016) 198-201.

[11] Rolo, M. D., Bugalho, R., Gonçalves, F., Mazza, G., Rivetti, A., Silva, J.C., Silva, R., Varela, J. *Tofpet asic for pet applications*, *Journal of Instrumentation* **8.02** (2013) C02050.

[12] Camarlinghi, N., et al. *An in-beam PET system for monitoring ion-beam therapy: test on phantoms using clinical 62 MeV protons*, *Journal of Instrumentation* **9.04** (2014) C04005.