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ORAL PRESENTATION

Experimental validation of the filtering approach for dose monitoring in proton therapy at low energy

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Abstract The higher physical selectivity of proton therapy demands higher accuracy in monitoring of the delivered dose, especially when the target volume is located next to critical organs and a fractionated therapy is applied. A method to verify a treatment plan and to ensure the high quality of the hadrontherapy is to use Positron Emission Tomography (PET), which takes advantage of the nuclear reactions between protons and nuclei in the tissue during irradiation producing β^+-emitting isotopes. Unfortunately, the PET image is not directly proportional to the delivered radiation dose distribution; this is the reason why, at the present time, the verification of depth dose profiles with PET techniques is limited to a comparison between the measured activity and the one predicted for the planned treatment by a Monte Carlo model. In this paper we test the feasibility of a different scheme, which permits to reconstruct the expected PET signal from the planned radiation dose distribution along beam direction in a simpler and more direct way. The considered filter model, based on the description of the PET image as a convolution of the dose distribution with a filter function, has already demonstrated its potential applicability to beam energies above 70 MeV. Our experimental investigation provides support to the possibility of extending the same approach to the lower energy range ([40, 70] MeV), in the perspective of its clinical application in eye proton therapy.

Introduction

Most efforts in external beam radiotherapy are aimed to achieve the deposition of higher radiation doses to the

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tumor regions sparing as much as possible the surrounding healthy tissues.

In this context, the irradiation with protons offers physical advantages over the common irradiation modalities, thanks to a reduced lateral spreading when penetrating in matter and to a localized dose deposition in depth.

However, the full clinical exploitation of proton selectivity could be hampered, even during the pre-treatment phase, by the difficulty in superimposing the dose distal fall-off on the tumor boundaries. Currently the treatment planning (TP) calculations can be affected by few percent range uncertainties, which are intrinsic to the usage of calibration curves between CT photon attenuation coefficients and proton stopping power [1]. Besides, since the total therapeutic dose is often delivered in more than one fraction, further different sources of errors may arise from daily setup variations, internal organ motions and anatomical or physiological changes. As a result, the availability of a dosimetry tool turns out to be a prerequisite for quality assurance in proton therapy.

A non-invasive method to verify the accuracy of treatment delivery is provided by Positron Emission Tomography. It is based [2–5] on the detection of the β^+-activity induced by nuclear reactions between incident particles and target nuclei. Unfortunately, due to the energy thresholds of the isotope activation reactions (typically 15–20 MeV), the distal 50% activity level is located few millimeters before the dose peak position. This fact, along with the different nature of the interactions leading to the isotope activations and the energy delivery, makes the dose reconstruction a non-trivial task.

The dose verification is usually limited to an indirect test: the measured PET image is compared with the simulated activity by means of a Monte Carlo (MC) code. However, a simpler and more direct way to reconstruct the expected PET signal from the planned radiation dose distribution has been recently tried out in [6], where a filtering approach is proposed to replace of the full-blown MC simulation use.

This work is focused on the possibility to apply this method to an unexplored energy range ([40, 70] MeV) which could be more critical with respect to higher energy ranges, because of the greater relative incidence of the uncertainties about the nuclear cross sections in the lower part of the energy spectrum. Moreover, due to a smaller relevance of the straggling at the energies which we are dealing with, any imprecision in the cross section peak positions survives to the straggling smoothening and therefore will be reflected in a more severe disagreement between theory and experimental observation.

The promising results obtained, that are shown in this paper, provide support to the hypothesis of the existence of a universal filter function to convert dose into activity profile whatever is the beam energy. This encourages the efforts to invert the filter itself and to obtain a direct information about dose localization.

The paper is organized as follows. In the Materials and methods we describe our experimental setup and the process of data collection performed at CATANA (Centro di AdroTerapia e Applicazioni Nucleari Avanzate) at INFN–LNS (Istituto Nazionale di Fisica Nucleare – Laboratori Nazionali del Sud) in Catania (Italy), where 62 MeV proton beams are employed for the treatment of ocular melanomas [7]. The achievable accuracy in range monitoring is presented and discussed in the Data analysis. In the Unfolding we briefly describe the filtering approach and the model we used to calculate the dose curve and the associated activity profile. The application of theoretical filter to measured activity images is reported in the Results and discussion, along with a new separation method of the activity contributions of several isotope species. The conclusions follow in the last section.

Materials and methods

The PET prototype

The dedicated PET prototype consists of two planar heads, each one providing an active area of about 5 cm × 5 cm. Each head is made up of a squared multianode photomultiplier (Hamamatsu H8500 [8]) coupled to a matrix of the same size of LYSO scintillating crystals (2 mm × 2 mm × 18 mm pixel dimensions). A multiplexed readout [9] is used to reduce the number of collected signals from each head to four signals, while dedicated, compact electronic boards are used for signal amplification and digitization. The data acquisition enables the storage of coincidences in list mode with a maximum count rate of about 50 kHz (and 200 kHz single events for each head).

Image reconstruction is achieved by a standard iterative maximum-likelihood expectation–maximization (ML–EM) algorithm [10]. To obtain optimal reconstruction results a dedicated system model is used within the ML–EM: it is setup using a multi-ray method [11] which takes into account the geometry as well as the physical aspects.

The system performances were estimated by means of a ^{22}Na point source with a diameter of 1 mm put at the center of the field of view (FOV) with the two heads positioned symmetrically with respect to the source at a distance of 14 cm from each other. A spatial resolution of 1.7 mm FWHM was obtained in the midplane of the tomograph. The coincidence detection efficiency of the system was found to be $\approx$1% in the energy window [150–850] keV.

The experiments

The feasibility of range monitoring was studied in monoenergetic and extended irradiations of homogeneous polymethyl-methacrylate (PMMA, $C_5H_8O_2$, $\rho = 1.19\ g/cm^3$) equilateral cylinders with a diameter of 7 cm. In all measurements the targets were placed in a symmetric configuration between the two planar heads. The position along the beam direction was chosen so as to place the distal fall-off of activity distribution in the center of FOV, where spatial resolution and sensitivity are maximum.

During each irradiation, a total dose of 30 Gy was delivered in 1–2 min with a proton beam intensity of about 10^7 p/s. The lateral spread was limited by a circular collimator of diameter of 25 mm. Modulated proton beams were produced using modulating wheels, whilst effective energies lower than 62 MeV were obtained by inserting PMMA range shifters of different thicknesses along the beam path. A plane–parallel Markus ion chamber was chosen as reference detector for the absolute dose measurements in

water phantom and a silicon diode was chosen for the relative ones.

The activated phantoms were imaged after the end of irradiation for an acquisition time of 30 min. The lower threshold of the acceptance energy window was set to 350 keV in order to have an efficient reduction of the background noise, due to the presence of β^--emitting nuclei (^{176}Lu) in LYSO scintillator. In this way it was possible to remove the random coincidences due to the 88, 202, and 307 keV γ lines emitted simultaneously to the beta particles, along with beta—gamma coincidence true events resulting from the production of the beta particle (with a mean energy of 420 keV) in one detector and the detection of a gamma photon produced in the same decay by the other one.

Data analysis

Feasibility and accuracy of PET dose monitoring

It is a plain issue that the first, most meaningful, information one hopes to recover through the PET image concerns the depth—dose profile rather than its transverse distribution.

Fig. 1 shows the lateral activity distributions as reconstructed for three spread-out Bragg peaks (SOBPs) of 10.8 mm plateau width. Range shifters were placed along the beam line so that each irradiation differs from the other ones only in the proton range, with variations less than 2 mm.

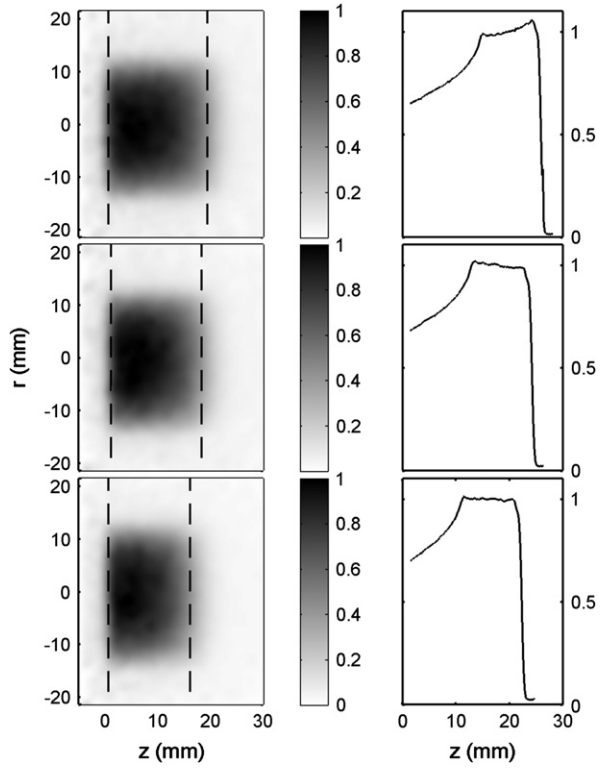

Figure 1 Reconstructed 2D activities (left boxes; gray color bar labels are normalized to the maximum) and related dose profiles (right boxes) for three shifted 10.8 mm SOBPs with a practical range of 26.4 mm, 24.7 mm and 23.7 mm, respectively; dashed lines mark the half-maximum activity depths.

The distal half-maximum activity depths were found to be 18.9 mm, 17.7 mm and 15.7 mm, respectively. Since the dose profiles are simply given by three different shifts of the same curve, a measure of the range monitoring accuracy is given by the constance of the difference between the practical beam range and the distal half-maximum activity depth. For the three set of measures, this difference is 6.6 mm, 5.9 mm and 7.0 mm, respectively, to which corresponds a standard deviation of 0.6 mm. This result supports the possibility to extract information on the maximum proton range with an accuracy of less than 1 mm, including the spatial resolution response of the PET detector and the position precision. Because of phantom positioning uncertainties with respect to the tomograph, a more precise measure of the activity fall-offs may be the activity FWHMs (18.8 mm, 17.1 mm and 15.6 mm, respectively), leading to a standard deviation of 0.3 mm.

As far as the lateral activity distribution and its correlation to dose are concerned, we observed that the former is well-correlated with the energy deposition because of the direct proportionality of both quantities to the particle fluency. The effective 50% isoactivity diameter is almost constant over the whole range of penetration depths and agrees with the corresponding isodose contour diameter (approximately 25 mm) within $\pm$1 mm. Hence, the lateral activity distribution turns out to be a good tracer of the collimator edge profile: this means that no significant beam divergence is observed.

Unfolding

The filtering approach

The method proposed in Ref. [6] relies on the description of the PET image as a convolution of the dose distribution with a filter function. At its basis there is the introduction of $\tilde{Q}_\nu(x)$ functions, defined as the convolution of a Gaussian with a power law function. The convolution integral has a closed form representation in terms of the parabolic cylinders functions [12,13] which depend on the parameter ν. In particular it has been proved that they are particularly suitable to approximate both the proton Bragg curve [12] and the related axial isotope (in off-line PET mainly ^{11}C and ^{15}O) density profiles. Since the convolution of an arbitrary $\tilde{Q}_{\nu_1}(x)$ with another $\tilde{Q}_{\nu_2}(x)$ is an endomorphism with a closed analytical expression, given a pair of dose and isotope curves (for instance, by a simulation toolkit), it is straightforward to analytically extract the expression of the filter (obviously resulting in another $\tilde{Q}$ function), that converts the dose into the specific isotope profile. Once shown that, for each isotope species, the filter is almost the same as the initial beam energy varies, it is possible to apply such a filter directly on an arbitrary dose profile to derive the induced isotope distribution. To obtain the observed activity distribution one simply applies a new filter to the dose curve, as resulting from the linear combination of each isotope filter. Each coefficient is obviously given by the fraction of isotopes of the species under investigation which decayed during the scansion time.

The model calculation

A phenomenological model was developed and implemented in MATLAB (The MathWorks, Inc., Natick, MA) environment to predict both the dose curve and the associated activity profile in a homogeneous medium for an arbitrary initial energy spectrum of the proton beam. It relies on a semi-analytical treatment of the evolution of the beam energy distribution along the path inside the target. Using an approach à la Fokker–Planck, it describes the Bethe–Bloch drift and the Vavilov diffusion in energy space of the initial spectrum. The sets of nuclear cross sections were interpolated from experimental data extracted from ''Experimental Nuclear Reaction Data File'' (EXFOR), maintained by National Nuclear Data Center at BNL [14]. The problem was factorized into a central axis evolution and a lateral spreading, according to the separation of the two main physical mechanisms that determine the effective 3D dose and specific activity. It is then possible to obtain a rather complete description of the effects the proton beam produces in the phantom. We underline once again that, in this context, only the axial dose and activity profiles are needed.

So far we considered only the main (p,pn) reaction channels on carbon and oxygen, leading to ^{11}C and ^{15}O production, respectively. These two reactions determine the shape of the activity profile in our phantom experiments. In the future we can easily extend our results to more complex biological targets which may contain also nitrogen.

Results and discussion

Testing the theoretical filters on experimental data

Fig. 2 shows the experimental β^+-activity depth profiles for a monoenergetic proton beam and two spread-out Bragg peaks of 10.8 mm and 17.9 mm plateau width, respectively, obtained by integrating the measured 3D-data over the entire lateral extension of the field. For comparison we superimpose the distributions obtained by applying the filter to the depth dose profiles, smoothed with a Gaussian point spread function of 1.7 mm FWHM to account for the spatial resolution of the PET prototype. In all the presented results, a very good agreement in depth position was found for the same activity level between the filter-calculated and the measured activity profiles.

The separation of isotope contributions

In order to deduce the relative amounts of ^{11}C and ^{15}O isotopes produced during irradiation and their contributions to the shape of the total activity profile, we performed a time analysis on the measured data. For each voxel of the reconstructed volume we followed the time evolution of the activity over the acquisition duration and fitted it by means of the linear combination of two exponential curves with decay times $\tau_{^{11}C} = 1.764 \times 10^3$ s and $\tau_{^{15}O} = 1.757 \times 10^2$ s. The coefficients provide the expected densities of isotopes in the voxel.

The results obtained for two different irradiations are shown in Fig. 3, along with the depth–densities profiles

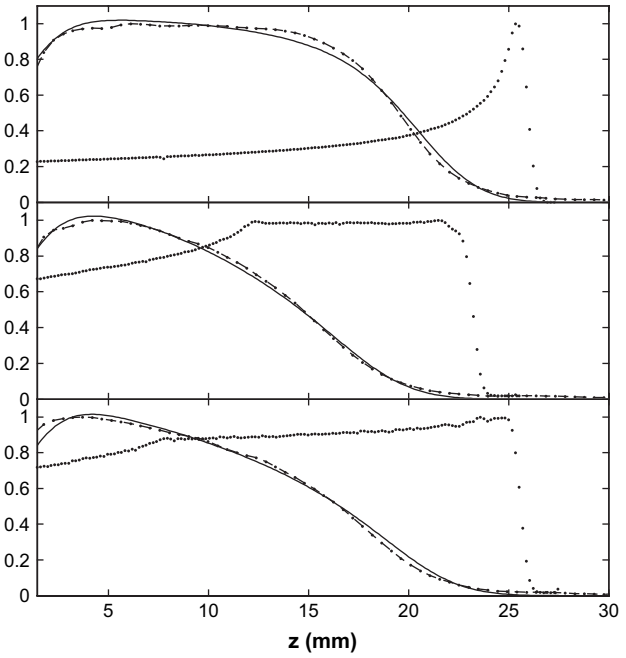

Figure 2 Reconstructed activity (dash-dot line) in comparison with the dose (dotted line) and the activity obtained by filtering the dose (solid line) for a monoenergetic irradiation (upper box), 10.8 mm SOBP (medium box) and 17.9 mm SOBP (lower box).

derived by filtering each measured depth–dose profile with the filters associated to the two isotopes. The relative contribution to the overall activity provided by each species, as inferred in this way, agrees very well in both magnitude and shape with the model expectations. In particular it is confirmed that only one quarter of the overall activity

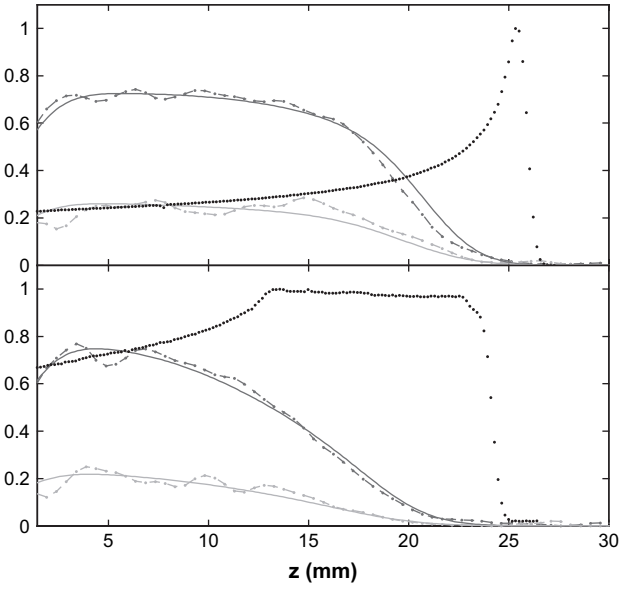

Figure 3 Isotope distributions for monoenergetic (upper box) and 10.8 mm SOBP (lower box). Estimated (dash-dot line) carbon (dark gray) and oxygen (light gray) distributions are compared with the dose (dotted line) and the isotope densities obtained by filtering the dose (solid line).

is due to oxygen, while the remaining 75% is provided by carbon. In spite of the low statistics, we obtained at once both a cross section validation and a verification of the filtering approach suitability.

Summary and conclusions

Proton dose monitoring with PET techniques and its application to proton radiotherapy has been investigated in the energy range [40, 70] MeV by the activation of PMMA phantoms, with promising results as for the achievable accuracy in range monitoring along beam direction.

The poor spatial correlation between the depth dose profiles and the corresponding depth activity profiles limits, at the moment, the dose verification to an indirect test. At the purpose, a novel approach for one-dimensional estimation of proton-induced activity has been validated against PET experimental data taken on homogeneous phantoms. The interesting aspect of this method consists not only in its simplicity, but also in the possibility of being turned into an instrument for direct verification of dose delivery from in situ PET activation.

The promising results obtained provide support to the hypothesis of the existence of a universal filter function converting, whatever the beam energy, dose into activity profile, thus encouraging the efforts to invert the filter itself to eventually pursue the proper dosimetric goal. Although the uniqueness of the filter could not exhaust the list of tests needed to claim its suitability for a direct dose monitoring (the recovering of the dose profile from the broader activity function by means of a simple inverse filter convolution may turn out to be a noise–unstable task), from our study it clearly emerges the applicability of this approach as an alternative to full-blown MC simulation for dose verification.

The generalization to inhomogeneous media, although not discussed here, can be easily achieved by stretching the spatial distribution to the equivalent path length in the material for which the filter functions are defined.

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