Secondary radiation measurements for particle therapy applications: charged particles produced by $^4$He and $^{12}$C ion beams in a PMMA target at large angle

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Abstract

Proton and carbon ion beams are used in the clinical practice for external radiotherapy treatments achieving, for selected indications, promising and superior clinical results with respect to x-ray based radiotherapy. Other ions, like $^4$He have recently been considered as projectiles in particle therapy centres and might represent a good compromise between the linear energy transfer and the radiobiological effectiveness of $^{12}$C ion and proton beams, allowing improved tumour control probability and minimising normal tissue complication probability. All the currently used p, $^4$He and $^{12}$C ion beams allow achieving sharp dose gradients on the boundary of the target volume, however the accurate dose delivery is sensitive to the patient positioning and to anatomical variations with respect to photon therapy. This requires beam range and/or dose release measurement during patient irradiation and therefore the development of dedicated monitoring techniques. All the proposed methods make use of the secondary radiation created by the beam interaction with the patient and, in particular, in the case of $^{12}$C ion beams are also able to exploit the significant charged radiation component.

Measurements performed to characterise the charged secondary radiation created by $^{12}$C and $^4$He particle therapy beams are reported. Charged secondary yields, energy spectra and emission profiles produced in a poly-methyl methacrylate (PMMA) target by $^4$He and $^{12}$C beams of different therapeutic energies were measured at 60° and 90° with respect to the primary beam direction. The secondary yield of protons produced along the primary beam path in a PMMA target was obtained. The energy spectra of charged secondaries were obtained from time-of-flight information, whereas the emission profiles were reconstructed exploiting tracking detector information. The obtained measurements are in agreement with results reported in the literature and suggests the feasibility of range monitoring based on charged secondary particle detection: the implications for particle therapy monitoring applications are also discussed.

Introduction

Ions deposit the maximum dose at the end of their range in tissue, the Bragg peak (BP), whereas they deposit an insignificant dose beyond the tumour and a much lower dose in their path towards the tumour, contrarily to...
x-rays that deposit their maximum dose close to the patient surface. The superposition of several Bragg curves creates the so-called spread-out BP covering the target volume with a homogeneous dose distribution. The dose deposition characteristic of ions gives the possibility to reduce the dose to normal tissue and spare organs at risk, and, as a result, the option to increase the dose in selected tumour regions. Light ions that are heavier than protons offer, additionally, an increased radiobiological effectiveness that makes particle therapy (PT) with, e.g. $^{12}$C ions favorable to treat radio-resistant tumours (Paganetti 2014, Tommasino and Durante 2015).

The results of clinical studies support the application of proton and $^{12}$C ion beams for cancer treatment (Allen et al 2012, Loeffler and Durante 2013, Kamada et al 2015, Durante et al 2017). Recent considerations on advances in PT include the application of $^4$He ion beams for more efficient treatment and increased life expectancy of pediatric patients. $^4$He ion beams potentially exhibit properties that are a compromise between those of protons and carbon ions, i.e. an increased radiobiological effectiveness and less lateral multiple scattering with respect to protons while having a lower beam fragmentation with respect to carbon ions (Kaplan et al 1994, Castro et al 1997, Tommasino et al 2015, Mairani et al 2016a, 2016b, Krämer et al 2016, Krämer et al 2017). However, scanned ion beam therapy has to account for inaccuracies related to possible anatomical changes, patient positioning and, finally, treatment planning, e.g. issues in the conversion of CT Hounsfield units to relative proton stopping power that are currently included in safety margins, used to extend the clinical target volume (CTV) to the planning target volume (PTV). Such inaccuracies may cause the BP position to be displaced during the treatment delivery with respect to the BP position predicted in the treatment plan, which is commonly referred as beam range (Knopf and Lomax 2013). This uncertainty limits the treatment accuracy, especially in the distal region where a reduction of the range uncertainty would allow the reduction of PTV safety margins and a better sparing of the organs at risk surrounding the target volume.

In order to fully exploit the advantages of ion beams in the clinical practice, the development of novel techniques to verify and/or monitor the beam range in the patient during the therapy is desirable. Several monitoring strategies based on the measurement of secondary radiation exiting the patient have been proposed. Different approaches based on prompt gamma (PG) detection were recently extensively reviewed by Krimmer et al (2017) presenting a detailed overview of the progress in PG development focusing on the rationale of PG techniques, modelling of the PG signal, detector prototypes (imaging and non-imaging systems), reconstruction strategies, challenges and clinical applicability. Recently PG based monitoring was applied, for the first time, in a clinical proton treatment (Richter et al 2016, Xie et al 2017, Verburg et al 2017) and clearly showed its potential to considerably improve the precision of PT. Detection of $\beta^+$ coincidence photons was clinically tested with diagnostic PET devices and widely investigated using dedicated detector systems, e.g. Parodi and Enghardt (2000), Agodi et al (2012b), Kraan et al (2014), Sportelli et al (2014) and Parodi (2015), whereas charged secondary fragments detection was evaluated experimentally and reported by Agodi et al (2012a), Henriquet et al (2012), Gwosch et al (2013), Piersanti et al (2014), Mattei et al (2017a) and Finck et al (2017). Considering the secondary radiation signal for different ion species, the number of PG with proton beams is $\approx 20$ times larger than for carbon-ion beams (Krimmer et al 2017). Therefore, it is unrealistic to achieve online verification of the carbon-ion range with millimetric precision at the pencil beam scale with the gamma cameras that are under development (Krimmer et al 2017). This is a rationale for the development of new range monitoring techniques for ions heavier than protons.

In this paper measurements of charged secondary particle production induced by $^4$He and $^{12}$C beams at therapeutic energies impinging on a target made of poly-methyl methacrylate (PMMA) are reported. The accurate measurement of the charged secondary particle yield is crucial in designing a range monitoring detector and optimizing its positioning with respect to the primary beam direction. A precise knowledge of the number of secondary particles produced per primary ion is also crucial to achieve the required resolution on the emission profile reconstruction for PT dose monitoring. In addition, the energy spectra of charged secondaries are needed to study the radiation signal exiting the patient accounting for tissue inhomogeneities, location of the tumour, treatment plan parameters and monitoring detector performance.

The experimental setup and data selection of the analysis are described in sections 1 and 2. Three crucial properties of the charged secondaries production were investigated: section 3 focuses on the yield measurements, section 4 on energy spectra, and section 5 on emission profiles.

For each primary ion beam the measured charged secondary emission profile was obtained. The implication of the results are discussed in view of few recently published papers (Reinhart et al 2017, Traini et al 2017, Battistoni et al 2017) that investigated the feasibility of range monitoring techniques in PT exploiting the detection of secondary charged particles.

1. Experimental setup

The experiment was performed in 2014 in the experimental cave of the Heidelberg ion beam therapy (HIT) centre, Germany, a hospital based facility using proton and carbon ion beams for patient treatment since 2009. The secondary radiation was detected at 60° and 90° with respect to the primary $^4$He ion beam impinging on the
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PMMA target, and at 90° with respect to a 12C ion beam (see figure 1, table 1). A constant PMMA length along the beam was used for 12C ion runs, whereas with 4He this length was adjusted according to the primary beam energy. Acquisitions with the 12C primary beam were performed with a fixed target length as these runs, unlike the acquisitions performed with 4He primary beams, did not aim at fragmentation and prompt-gamma signal studies, and were considered as a benchmark and supplementary to the data previously published in Piersanti et al (2014) and Mattei et al (2017a). The reference frame is depicted in figure 1: the beam direction is referred to as z, whereas x and y define the transverse plane with respect to the beam. The complete geometry of the experimental setup was implemented in the FLUKA (Ferrari et al 2005, Boehlen et al 2014) Monte Carlo (MC) code to simulate and study detector acceptance, efficiency and particle identification.

The PMMA target (5 × 5 cm² face orthogonal to the beam line, density 1.19 g cm⁻³, ionisation potential 74 eV—the material characteristic applied in MC simulations) was positioned at the beam isocentre ∼1 m away from the beam nozzle and with its longer side (target length, referred in the following as d_{PMMA}) along the beam line (figure 1).

A pencil beam with Gaussian spot size was used, with full width at half maximum (FWHM) ranging from 4.7 to 9.3 mm depending on the beam and its energy (see table 1). For each 4He primary beam energy, the PMMA target length d_{PMMA} along the beam was selected to keep the position of the BP ≃1 cm inside the PMMA, before its exit face. Table 1 lists the primary beam energy, range in PMMA (computed by FLUKA MC simulations) and transverse size (FWHM) as well as the d_{PMMA} PMMA length used in the experiment, as indicated in figure 1. When acquiring data with the 12C beam, a unique 10 cm long PMMA target was used. The most energetic 12C beam (220 MeV u⁻¹) stopped close to the target end, whereas less energetic 12C ion beams were stopped before the PMMA target, in between the PMMA entrance face and the origin of the reference frame.

The number of primary ions and the primary beam rate impinging on the PMMA target were measured using a 0.2 cm-thick plastic scintillator (start counter—SC; figure 1) positioned upstream at 37 cm from the PMMA target and read out by two opposite photomultiplier tubes (PMT; Hamamatsu H10580). The secondary particles produced in the target were studied using three isocentrically positioned detectors that were mounted on a movable arm: 0.1 cm-thick plastic scintillator (LTS), 21 cm-long drift chamber (DCH) and a matrix of four

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**Table 1.** Beam and setup properties used in the measurements; B_{FWHM}—spot size, Range—beam range in PMMA, d_{PMMA}—PMMA length along the beam, θ—detector angle with respect to the primary beam direction.

| Ion | Energy (MeV u⁻¹) | B_{FWHM} (mm) | Range (cm) | d_{PMMA} (cm) | θ |
|-----|-----------------|---------------|------------|---------------|---|
| 12C | 120             | 7.9           | 2.9        |               |   |
|     | 160             | 6.2           | 4.8        |               |   |
|     | 180             | 5.5           | 6.0        | 10.0          | 90° |
|     | 220             | 4.7           | 8.3        |               |   |
| 4He | 102             | 9.3           | 6.7        | 7.7           | 60° |
|     | 125             | 7.8           | 9.7        | 10.0          |    |
|     | 145             | 6.9           | 12.5       | 12.7          | 90°−60° |

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**Figure 1.** Experimental setup used for the measurement of charged secondary products generated by primary beam impinging the PMMA target (not to scale). DCH and LYSO detectors were mounted on a movable arm situated for different measurements at θ = 60° or θ = 90° with respect to the primary beam direction. The origin of the reference frame is marked by the black spot inside the PMMA target, ∼1 cm before the distal edge of PMMA box.
cerium doped lutetium–yttrium oxyorthosilicate crystals (LYSO), $1.5 \times 1.5 \times 12 \text{ cm}^3$ each. The position of the LTS, DCH and LYSO detector front faces with respect to the PMMA central axis were 8.0 cm, 50.5 cm (90°) and 55.0 cm (60°), 73.5 cm (90°) and 78.0 cm (60°), respectively. The scintillation light of LYSO crystals was detected with a single PMT (EMI 9814B PMT). The response of LYSO crystals was evaluated with the HIT accelerator proton beam. The crystal matrix was centred in front of the beam nozzle, parallel to a Gaussian shaped beam that was broad enough to expose the four crystals to the same average proton yield, and was irradiated with proton beams of seven energies in the 50–200 MeV range. The LYSO crystals showed a different light yield response, as shown in Mattei et al. (2017a), that had to be taken into account using the information from the DCH detector to assign each fragment to the relative crystal. The charge response of the different crystals was equalized when tuning the particle identification selection algorithms and cuts allowing the definition of a single set of PID bands for all the fragments regardless of the associated crystal (see next section).

The production point of the charged secondaries was obtained by three-dimensional reconstruction of the particle track with the DCH (Abou-Haidar et al. 2012), consisting of six alternating horizontal ($x-z$ plane) and six vertical ($y-z$ plane) wire layers, operated by applying a high voltage of 1.8 kV to the sense wires and flushing the active volume with an Ar/CO$_2$ (80/20) gas mixture, as described in Piersanti et al. (2014). In this configuration the single cell spatial resolution was 200 $\mu$m and the single cell efficiency was $\approx 96\%$. The readout and performance of the DCH as well as the tracking algorithm and calibration procedure can be found elsewhere (Agodi et al. 2012a).

The triggering logic implemented for the selection of charged secondaries required SC and LYSO signals coincidence within the 80 ns time window. The front-end electronics, used to acquire time and charge information from the described detectors, was read out by a VME system interfaced with a PC data acquisition (DAQ) server, as described in Piersanti et al. (2014). At the highest delivered beam rate of $\sim 3$ Mcps, the trigger rate was in the 0.3–6 kcps range, depending on the beam type and energy.

2. Data selection and particle identification

The selection of charged secondaries was performed by exploiting DCH information together with the energy released in the LYSO detector and the time of flight (TOF) defined as the time difference between LTS and LYSO detector signals.

Events containing charged secondary fragments candidates were selected requiring at least eight hits in the DCH: four hits in each view, translating in the requirement that at least four planes, out of the six available, in each view contained a valid signal. This selection ensures high efficiency for fragments detection given the high DCH single cell efficiency and the small emission angle ($\lesssim 10^\circ$) of charged fragment tracks that can trigger the DAQ while reducing neutral particles background to a negligible level.

Figure 2 illustrates the number of events as a function of the charge readout from the LYSO detector and the TOF. All the events collected with the carbon ion beam and the 90° configuration (a), as well as helium ion beam with 90° (b), and 60° (c) setup configuration ($N_{\text{DCH}} \geq 8$; all the investigated energies) are shown. The three bands characteristic of proton (P), deuteron (D) and triton (T) events are visible. The population of events with TOF $\sim 3.5$ ns and energies up to few MeV u$^{-1}$ was identified as electrons. Such a result is confirmed by data/MC comparison.

The identification of the fragments was performed using particle identification (PID) algorithms that used as input the charge signal from the LYSO crystals and the TOF. Selection bands for proton, deuteron and triton populations as indicated in figure 2 (bold lines) were defined. The central and most populated region, relative to the proton component, was used to model an analytic function capable of describing the peak position as a function of the TOF. This function was shifted, using an iterative procedure, in order to define a band, looking at the sliced charge projections as a function of the TOF. The dashed lines between the protons and deuteron bands correspond to the region, identified in the sliced projections, in which the charge distributions looked flat between the proton and deuteron peaks. The other bands (lower discrimination of protons against other charged particles background and upper discrimination of deuteron and triton populations) were drawn by eye, shifting the proton bands, aiming for a conservative evaluation of the possible cross feed among different particle hypotheses. The identity of the fragments was assigned accordingly to the band definition. The deuteron contribution was 5% and 10% of all events (P + D + T) detected at 90° and 60°, respectively, whereas the T contribution is at the level of 1–2% in all cases. In order to account for the underlying background contribution from neighbouring populations (e.g. deuteron background in proton distribution), the yields were re-evaluated using only the candidates falling in the regions defined by the dotted and small-dashed bands, accounting for the uncertainty related to the PID band definition and for the cross feed among the different populations.

The distributions shown in figure 2 were obtained with a number of primary ions $N_{\text{C ion}} = 3.3 \times 10^6$, $N_{\text{He ion}} = 8.6 \times 10^6$ and $N_{\text{He ion}} = 6.9 \times 10^6$ for (a), (b) and (c) configurations, respectively. The number of incoming ions for each data sample were: 1.2, 0.8, 0.5 and 0.7 billion of $^{12}\text{C}$ ions, respectively, for the 120, 160, 180
and 220 MeV energies; 2.8, 2.9 and 2.9 billion of $^4\text{He}$ ions, respectively, for the 102, 125 and 145 MeV energies detected at $90^\circ$; 3.7 and 3.2 billion of $^4\text{He}$ ions, respectively, for the 125 and 145 MeV energies detected at $60^\circ$. For the three different configurations a total number of secondary particles ($P + D + T$) equal to 3753, 4676 and 51711 was measured.

3. **Yield and efficiency evaluation**

The significantly larger statistics and the greater kinetic energy per nucleon of the proton component of the secondary radiation, with respect to deuteron and triton, makes the former more interesting for monitoring purposes. We have hence focused on this component in the following. The differential production rate of secondary protons, normalised to the number of primary ions, averaged on the total solid angle and integrated over the full target length (i.e. yield) was estimated, for helium and carbon ion beams, as:

$$\Phi_p = \frac{dN_p}{N_{\text{ion}} d\Omega} = \frac{1}{4\pi} \frac{1}{N_{\text{ion}} \epsilon_{\text{DT}}} \sum_{E_{\text{kin}}} \sum_{z} N_{p}(E_{\text{kin}}, z) \epsilon_{p}(E_{\text{kin}}, z),$$

where $N_{p}(E_{\text{kin}}, z)$ is the number of detected protons, $N_{\text{ion}}$ is the number of primary ions impinging on the PMMA target, $\epsilon_{\text{DT}}$ is the dead time (DT) efficiency, and $\epsilon_{p}(E_{\text{kin}}, z)$ is the total detection efficiency computed as a function of the production point ($z$) and of the kinetic energy ($E_{\text{kin}}$) of secondary particles. The TOF between LTS and LYSO detectors was used to measure $E_{\text{kin}}$ of detected secondary particles, whereas their production point in PMMA was reconstructed using DCH information.

The total number $N_{\text{ion}}$ of primary ions impinging on the PMMA target is computed counting the number of SC signals and correcting for dead time efficiency introduced by the electronics needed to generate the trigger signals. The correction factor and its systematic uncertainty was obtained specifically for each run from the dedicated MC simulations accounting for the complete setup geometry. The DT efficiency was evaluated using the VME system, counting all the generated trigger signals ($N_{\text{TrAcq}}$) and the trigger signals actually acquired by the DAQ system ($N_{\text{TrTot}}$). The efficiency defined as $\epsilon_{\text{DT}} = N_{\text{TrAcq}}/N_{\text{TrTot}}$ varied from 60% to 90%, depending on the beam rate. Run specific values of $\epsilon_{\text{DT}}$ were used to compute the yields using equation (1) for the different data acquisition conditions: primary ion beam, beam energy and angular configuration.

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The total proton detection efficiency $\epsilon_{p}(E_{\text{kin}}, z)$ including detector efficiencies (LTS, DCH, LYSO) was computed from a dedicated MC simulation accounting for the complete setup geometry. $\epsilon_{p}(E_{\text{kin}}, z)$ varies as a function of the production point ($z$) of secondary particles, due to the geometrical acceptance of the DCH–LYSO system and as a function of the kinetic energy ($E_{\text{kin}}$) of secondary particles. This last dependency is primarily due to the energy lost to escape the PMMA and to the primary beam spot size in the transverse plane. The efficiency evaluation has been performed using a customised version of the MC simulation in which protons and deuterons were directly generated inside the PMMA phantom with a flat energy distribution (in the $E_{\text{kin}}^{\text{prod}} = 10–250$ MeV range) and a flat spatial distribution along the $z$ axis (coordinate system introduced in figure 1). FLUKA was
used only to simulate the transport of protons generated within the PMMA, towards the LYSO detector, and we were hence completely independent of the charged fragments production model used in the full simulation to describe the interactions of the primary ion beam with the target.

The efficiency map \( \epsilon_{p}(E_{\text{kin}}^{\text{Det}}, z) \) was also built with another method generating secondary protons in PMMA at ten fixed energies in the range \( E_{\text{kin}}^{\text{Prod}} = 50–250 \text{ MeV} \) and assuming a flat spatial distribution along the \( z \) axis. The number of detected protons was counted at ten detection energies \( (E_{\text{kin}}^{\text{Det}}) \), and at these energies the efficiency distribution \( \epsilon_{p}(E_{\text{kin}}^{\text{Det}}, z) \) was calculated. The efficiency values between different detection energies \( E_{\text{kin}}^{\text{Det}} \) were built using an interpolation procedure in 10 MeV energy steps accounting for their production position in PMMA along the \( z \) axis in 5 mm steps. The difference observed between \( \epsilon_{p}(E_{\text{kin}}^{\text{Det}}, z) \) obtained using the two methods was used to assign a systematic uncertainty to the efficiency evaluation.

The total detection efficiency map \( \epsilon_{p}(E_{\text{kin}}^{\text{Det}}, z) \) obtained from MC simulation is shown in figures 3(b) and (e) for 90° and 60° setup configurations, respectively. The detection efficiency of particles with lower \( E_{\text{kin}}^{\text{Det}} \) values \((0–40 \text{ MeV} ; \text{blue area in figures 3(b) and (e)})\) is smaller than the detection efficiency of the more energetic particles. Particles with low \( E_{\text{kin}}^{\text{Det}} \) are less likely to exit the PMMA, depending on their production point: the minimal \( E_{\text{kin}}^{\text{Prod}} \) needed to exit the PMMA depends mainly on the particle’s production point in the \( x–y \) plane. The average minimal production energy of protons needed to exit PMMA was estimated from MC simulation to be about \( E_{\text{kin}}^{\text{Prod}} \approx 50 \text{ MeV} \) (see section 4 and figure 5).

The proton yield \( (\Phi_{p}) \) over the detection threshold \( (E_{\text{kin}}^{\text{Prod}} > 50 \text{ MeV}) \) was obtained from the number of detected protons \( (N_{p}) \) as a function of the production point \( (z) \) and the detected kinetic energy \( (E_{\text{kin}}^{\text{Det}}) \), as illustrated in figure 3. The number of measured events in each bin \((N_{p}(E_{\text{kin}}^{\text{Det}}, z), \text{figures 3(a) and (d)})\) was corrected for the efficiency \( \epsilon_{p}(E_{\text{kin}}^{\text{Det}}, z) \) figures 3(b) and (e)) providing the yield for each bin of kinetic energy \( (E_{\text{kin}}^{\text{Det}}) \) and production point \( (z) \) \( \Phi_{p}(E_{\text{kin}}^{\text{Det}}, z), \text{figures 3(c) and (f)})\). The integrated number of events corrected for total detection efficiency, dead time efficiency and normalised to the number of primaries shown in figures 3(c) and (f) corresponds to the proton yield \( (\Phi_{p}) \) given in table 2.

Figure 4 shows \( \Phi_{p} \) as a function of \(^{12}\text{C}\) and \(^{4}\text{He}\) ion beam energy and for the detector positioned at 90° and 60° with respect to the primary beam direction. The measured yields are reported with both statistical and systematic uncertainties in table 2. The number of secondary particles produced in the target increases with the energy of the primary beam, i.e. with its range. Comparing ion beams having a similar range, the yield produced by the \(^{12}\text{C}\) ion beam at 220 MeV \( \text{u}^{-1} \) is higher than the one produced by the \(^{4}\text{He}\) beam at 125 MeV \( \text{u}^{-1} \), as the secondary particles that have the kinetic energy necessary to exit the target are produced essentially in projectile fragmentation. The secondary particle yield induced by \(^{4}\text{He}\) ion beam of a similar range and detected at 60° with respect to the primary beam direction is one order of magnitude higher than the secondary particle yield detected at 90°.

The total uncertainty on the measured yield consists of both statistical and systematic contributions. Fractional statistical uncertainty ranges from 1% to 7% depending on the primary ion beam, its energy and setup configuration (90° or 60°) and is mainly due to the statistical fluctuation on the number of detected charged secondary particles. The fractional statistical uncertainty contribution from both the detection efficiency (due to the MC sample statistics) and the number of primary ions is at few per mil level.

The fractional systematic contribution generally dominates the yield uncertainty and ranges from 12% to 22%. The main contribution comes from the efficiency map estimation method and ranges from 8% to 19%. The systematic uncertainty related to the correction to the total number of primary ions (Mattei et al 2017b), estimated from a dedicated MC simulation, is a function of the primary ion beam rate and is within the 2%–7% range. The systematic uncertainty related to the calculation of the raw number of the primary ions was assessed with independent ion counting method using the external PET detectors available during the data taking, as described in detail elsewhere (Mattei et al 2017b), and ranges from 4% to 6%. The systematic uncertainty related to PID selection algorithms (figure 2) ranges from 3% to 6%. The systematic uncertainty related to less and more rigorous DCH selection criteria \((N_{\text{DCH}} \geq 7 \text{ or } N_{\text{DCH}} \geq 9)\) is negligible. The contribution from the DT correction is also negligible.

The yield obtained with primary carbon ion beam at 220 MeV \( \text{u}^{-1} \) and applying the same selection criteria as in Piersanti et al (2014), Mattei et al (2017a) is \( (2.80 \pm 0.08^{\text{stat}} \pm 0.21^{\text{sys}}) \times 10^{-3} \text{ sr}^{-1} \). This result is in agreement with uncertainties in the total yield \( (2.74 \pm 0.02^{\text{stat}} \pm 0.17^{\text{sys}}) \times 10^{-3} \text{ sr}^{-1} \) obtained by Piersanti et al (2014) and Mattei et al (2017a).  

4. Energy spectra

The kinetic energy distribution of secondary particles is crucial information to be exploited for range monitoring purposes. Charged secondary particles cross several centimeters of patient’s tissue before exiting the body, losing kinetic energy and undergoing multiple scattering (MS). Therefore modelling and quantifying these effects is one of the challenges of ion beam therapy monitoring based on charged secondaries detection.
In this study, the detected kinetic energy of secondary protons measured after their exit from the PMMA target \( (E_{\text{Det}}^{\text{kin}}) \) is reported. The detected kinetic energy \( (E_{\text{Det}}^{\text{kin}}) \) can be related to the proton kinetic energy at production \( (E_{\text{Prod}}^{\text{kin}}) \) considering the energy loss in the PMMA obtained from high statistics MC simulation, as shown in figure 5. A total number of \( 3.0 \times 10^9 \) protons was produced in the PMMA target uniformly in the \( z \) direction and isocentrically in the transversal plane, with the FWHM \( = 1 \) cm and in the energy range \( 10 \text{–} 250 \) MeV. The uncertainty in the transformation from \( E_{\text{Prod}}^{\text{kin}} \) to \( E_{\text{Det}}^{\text{kin}} \) results from the the distance in the PMMA material that particles have to go through to exit the target. Such distance depends on the distance in the PMMA material that particles have to go through to exit the target. Such distance depends also on multiple scattering of secondary protons in the target.

In order to use secondary protons for monitoring purposes, the crossing of some centimetres of patient’s tissue has to be considered and therefore the range \( E_{\text{Prod}}^{\text{kin}} > \) few tens of MeV of the detected kinetic energy distribution is the most interesting for the above-mentioned application (Agodi et al 2012a).

Table 2. Yields of secondary protons \( (\Phi) \) for carbon and helium ion primary beams. The table includes information about the primary ion beam (Beam), its kinetic energy per nucleon (Energy) and setup configuration (\( \theta \)) used for the measurements.

| \( \theta \) | Beam | Energy (MeV u\(^{-1}\)) | \( \Phi \) \( ± \sigma_{\text{stat}} \) \( ± \sigma_{\text{sys}} \) (10\(^{-3}\) sr\(^{-1}\)) |
|---|---|---|---|
| 90\(^{\circ}\) | \(^{12}\)C | 120 | 0.49 \(±0.03\) \(±0.06\) |
| | | 160 | 1.44 \(±0.06\) \(±0.18\) |
| | | 180 | 2.16 \(±0.10\) \(±0.26\) |
| | | 220 | 4.49 \(±0.13\) \(±0.59\) |
| 60\(^{\circ}\) | \(^{4}\)He | 125 | 0.96 \(±0.03\) \(±0.12\) |
| | | 145 | 1.75 \(±0.04\) \(±0.20\) |
| 4\(^{\circ}\)He | 102 | 4.59 \(±0.07\) \(±0.95\) |
| | 125 | 10.48 \(±0.10\) \(±2.19\) |
| | 145 | 17.49 \(±0.14\) \(±3.83\) |

Figure 3. Data ((a), (d)): the number of secondary protons (raw data) produced by the \(^{4}\)He beam at 145 MeV u\(^{-1}\). Respectively, 2.9 and 3.2 billion of \(^{4}\)He ions were collected to produce the raw distributions shown in (a) and (d). MC ((b), (e)): the efficiency maps obtained from MC simulations for secondary protons. Data corrected ((c), (f)): \( \Phi_{p}(E_{\text{Det}}^{\text{kin}}, z) \) — the secondary proton yield for the \(^{4}\)He beam at 145 MeV u\(^{-1}\). The data are plotted as a function of the detected kinetic energy \( (E_{\text{Det}}^{\text{kin}}) \) and reconstructed production point \( (z) \). The top ((a)–(c)) and bottom ((d)–(f)) plots illustrate the results obtained with detector positioned at 90\(^{\circ}\) and 60\(^{\circ}\) with respect to the primary beam, respectively. The energy spectra reported in section 4 were built from a profile of the right plots ((c), (f)) on \( y \)-axes. The emission shapes reported in section 5 were built from a profile of the left plots ((a), (d)) on \( x \)-axes.
Figure 6 shows the measured yields of secondary protons for the $^{12}\text{C}$ ion beam and the $^4\text{He}$ ion beam as a function of their detected kinetic energy $E_{\text{Det}}^{\text{kin}}$, obtained using the TOF measurements performed with LTS and LYSO crystal signals. The number of secondary particles produced in the target increases and their energy spectrum widens with the energy of the primary beam, i.e. with its range. For each primary beam energy, the yield integrated over all kinetic energies of secondary protons in figure 6 is equal to the total yield reported in table 2.

5. Emission profiles of detected fragments

Using DCH information, charged secondary particles were back-tracked to the PMMA target. The longitudinal emission profile of charged secondaries produced by the therapeutic beam (z-profile; figure 7) was built considering all the reconstructed tracks. The correlation between the BP position of a $^{12}\text{C}$ ion beam and charged secondary emission profile has already been shown (Agodi et al 2012a, Henriquet et al 2012, Gwosch et al 2013, Piersanti et al 2014, Mattei et al 2017a). We investigated the emission spectra for the $^{12}\text{C}$ ion and $^4\text{He}$ ion beams at all the energies. The charged secondary emission shape varies with the primary ion beam energy for both $^{12}\text{C}$ and $^4\text{He}$ (figure 7). As an example figure 7(d) shows the dose released by the $^4\text{He}$ ion beam at 125 MeV u$^{-1}$ overlapped with the reconstructed z-profile.
For each ion beam energy, the emission profile of charged secondaries was reconstructed and a chi-square fit was performed using a double Fermi Dirac (DFD) function (figure 7(e)) as introduced in Piersanti et al (2014):
\[
f(x) = P_0 \frac{1}{1 + \exp\left(\frac{x - p_3}{p_2}\right)} \frac{1}{1 + \exp\left(-\frac{x - p_3}{p_4}\right)} + P_5.
\]  
(2)

The fit parameters \(p_3\) and \(p_1\) are respectively related to the position of the rising and falling edge of the distribution, while \(p_2\) and \(p_4\) describe the rising and falling slopes of the function, whereas \(p_5\) models a flat background contribution. The parameters of the distribution characterising the emission shape are shown in figure 7(e), extracted and listed in tables 3 and 4 for different ion beams and beam energies:

- \(X_{\text{left}}\) parameter corresponds to the rising edge of the emission shape and indicates the PMMA entrance face position (\(EF_{\text{PMMA}}\)),
- \(\delta_{40}\) parameter is correlated to the range \(R\) of the primary beam.

The uncertainty on \(EF_{\text{PMMA}}\) and \(R\) is negligible.

The \(^{12}\text{C}\) beam, at each of the investigated energies, entered the 10 cm long PMMA target at the same position, as indicated by the rising edge of the emission profile (\(X_{\text{left}}\); figure 7(a); table 3).

Decreasing the energy of the \(^{12}\text{C}\) ion beam, the emission profile becomes shorter and the slope of its falling edge becomes steeper, as the production of the secondaries decreases with the range of the primary ion beam (see \(R\) and \(\delta_{40}\) parameter in table 4).
Differently from the $^{12}$C beam, for each energy of $^{4}$He beam the length of the PMMA target was adapted in such a way that the BP position was before the distal end of the target (see table 1). The beam entrance face was at different positions, as indicated both by the rising edge of the emission profile (figures 7(b) and (c)) and the $X_{\text{left}}$ parameter value of the emission shape (table 3). To demonstrate the feasibility of range monitoring with charged secondary profiles, the emission shape parameters were extracted. The difference between the expected and measured PMMA entrance face position ($EF_{\text{PMMA}} − X_{\text{left}}$) as well as the difference between the range $R$ and the $\delta_{40}$ parameter are listed in tables 3 and 4, respectively. The reconstructed $z$-profile, and corresponding parameters $X_{\text{left}}$ and $\delta_{40}$, vary depending on the incoming beam specific properties (e.g. beam spot size) and angular configuration of the detector, as an effect of MS. Furthermore, the fitted parameters have a correlation with the charged fragments production cross section and hence with the beam type. For this reason, beams of different type and different detection angles have to be studied separately in order to identify the set of function parameters that better describes the emission shape and can be correlated to entrance point and BP position. In the following study the analysis strategy optimised

Figure 7. Longitudinal profile of charged secondary fragments reconstructed inside the PMMA target. In figures (a), (d) and (e) the beam entrance face is at $-9.0$ cm, whereas in figures (b) and (c) the beam entrance face is at $-11.7, -9.0, -6.7$ cm for the $^{4}$He beam at 145, 125 and 102 MeV u$^{-1}$, respectively. The histograms have been normalized to the same maximum value (set to 1 in arbitrary units). The number of incoming ions used to produce the histograms is reported at the end of section 2. Figure (d) illustrates the $z$-profile (charged Emission—solid line) for $^{4}$He beam at 125 MeV u$^{-1}$ detected at $90^\circ$ (middle distribution from figure (b)) and the corresponding dose released inside the target. The released dose distribution (hatched area) was obtained from the MC simulation. The parameters of the emission profile shown in figure (e) were estimated based on a 40% threshold (horizontal dotted line), as introduced in Piersanti et al (2014). (a) The $^{12}$C beam, $90^\circ$ configuration. (b) The $^{4}$He beam, $90^\circ$ configuration. (c) The $^{4}$He beam, $60^\circ$ configuration. (d) The $^{4}$He beam at 125 MeV u$^{-1}$, $90^\circ$ configuration. (e) The $^{4}$He beam at 125 MeV u$^{-1}$, $90^\circ$ configuration.

Table 3. Emission shape parameter $X_{\text{left}}$ extracted from the fit of the emission shape with a DFD function and related to the expected entrance face $EF_{\text{PMMA}}$ of the PMMA target. The number of incoming ions used to produce these results is reported at the end of section 2.

| $\theta$ (°) | Ion (MeV u$^{-1}$) | Energy (MeV) | $EF_{\text{PMMA}}$ (cm) | $X_{\text{left}}$ (cm) | $EF_{\text{PMMA}} − X_{\text{left}}$ (cm) |
|-------------|---------------------|--------------|--------------------------|--------------------------|----------------------------------|
| $90^\circ$ | $^{12}$C | 120 | $-9.0 \pm 0.1$ | $-9.4 \pm 0.2$ | $0.4 \pm 0.2$ |
| | | 160 | $-9.3 \pm 0.1$ | $0.3 \pm 0.1$ | |
| | | 180 | $-9.1 \pm 0.1$ | $0.1 \pm 0.1$ | |
| | | 220 | $-9.3 \pm 0.1$ | $0.3 \pm 0.1$ | |
| $90^\circ$ | $^{4}$He | 125 | $-9.0 \pm 0.1$ | $-9.2 \pm 0.1$ | $0.2 \pm 0.1$ |
| | | 145 | $-11.7 \pm 0.1$ | $-11.7 \pm 0.1$ | $0.0 \pm 0.1$ |
| $60^\circ$ | $^{4}$He | 102 | $-6.7 \pm 0.1$ | $-7.5 \pm 0.1$ | $0.8 \pm 0.1$ |
| | | 125 | $-9.0 \pm 0.1$ | $-9.8 \pm 0.1$ | $0.8 \pm 0.1$ |
| | | 145 | $-11.7 \pm 0.1$ | $-12.5 \pm 0.1$ | $0.8 \pm 0.1$ |
for carbon ion beams and a 90° detection has been applied to helium ion beams at different angles. In particular, the definition of $X_{\text{left}}$ and $\delta_{40}$ is exactly the one introduced in Piersanti et al (2014) for all datasets.

The difference between the expected and measured PMMA entrance face position ($E_{FP_{\text{PMMA}}}-X_{\text{left}}$) is remarkably constant and consistent with zero within the uncertainty for the 90° samples, for both the $^{12}$C and $^4$He beams. Instead at 60° a systematic shift of 8 mm was observed: the value is constant against the different energies that were used to collect the data. Such a shift is a consequence of the use of $X_{\text{left}}$ as defined in Piersanti et al (2014), and optimised for the 90° analysis for which there is no contribution from the folding of the beam lateral spread with the depth of interaction with the PMMA phantom, as such dependence can be observed only for angles different from 90°.

A dedicated characterisation of helium ion beam related secondary production is ongoing to provide an optimised parameter that can be correlated with the entrance point and the BP position at different detection angles.

The difference between the expected and measured BP position ($R-\delta_{40}$) is constant and consistent with zero within the uncertainty for $^{12}$C emission profiles. For emission profiles obtained with $^4$He beams the difference between the expected and measured BP position ($R-\delta_{40}$) exceeds the uncertainty on the $\delta_{40}$ parameter evaluation. While the relation between $R$ and $\delta_{40}$ is evident for $^4$He beams, the selection of a parameter different from $\delta_{40}$ or a calibration of the $(R-\delta_{40})$ relation as a function of energy is necessary to provide an unbiased observable correlated with the BP position.

Nevertheless it is worth noticing the possibility of identifying patient mispositioning by measuring the $X_{\text{left}}$ parameter both for $^{12}$C and $^4$He beams.

Collected data indicate that charged secondary particles produced by $^{12}$C and $^4$He beams could be exploited for range monitoring purposes in hadron therapy, confirming the findings reported by Piersanti et al (2014).

### 6. Discussion

Results on the analysis of charged secondary particles produced by $^4$He and $^{12}$C ion beams impinging on a PMMA target were reported, measuring secondary particle yields, energy spectra and emission shapes as a function of the primary beam energy in a range interesting for PT applications. Yields of charged secondary particles detected at 90° and 60° with respect to the primary beam direction were obtained, correcting for detection efficiency as a function of the kinetic energy, as well as the production position of secondary particles. The secondary proton yield ranged from 0.5 to $17.5 \times 10^{-3}$ sr$^{-1}$ per primary ion depending on the primary ion beam, its energy and setup configuration (90° or 60°). Statistical and systematic uncertainty were assessed and the total fractional uncertainty estimated to be in the 12%–22% range. The energy spectra of charged secondary protons normalized to the number of primary ions were obtained. The emission point of each detected secondary particle was reconstructed to build the charged secondary emission profiles that were then correlated with the expected primary beam range.

In this manuscript we presented the study performed using a homogeneous PMMA target irradiated to characterise the production of secondary particles in therapeutic-like conditions. The obtained results are important for any study that aims to investigate a charged fragments based detection approach for monitoring applications in PT treatments performed with ions heavier than protons. The manuscript presents the measured abundance, kinetic energy spectra and emission profile of the detected charged fragments, either for $^{12}$C ion beams where the results are in good agreement with what expected from previous experimental campaigns or for the newly studied $^4$He beams. Such information is essential input for in silico studies on patient CT data needed to assess the feasibility of range monitoring based on charged secondary particle detection.
As a general remark we observe that the accuracy of any beam range monitoring based on charged secondary emission shape depends on the MS interactions undergone by the fragments inside the patient and on the collected sample statistics. Furthermore the detection angle should be optimised in order to have large secondary fragment statistics (increasing at forward angles) while considering at the same time the effect of a non-negligible transverse beam dimension degrading the longitudinal resolution on the BP position for very forward angles.

Finally, when discussing a clinical case, it is necessary to account for the proton population absorption undergone along the exit path, the MS undergone by the protons inside the body and the different secondary production rates in tissues of different density and atomic composition. The discussion on the accuracy attainable in monitoring the BP position in such realistic conditions is beyond the scope of this manuscript and is discussed in detail in other articles (Reinhart et al 2017, Traini et al 2017, Battistoni et al 2017), as summarized in the next section.

7. Conclusions

At the Heidelberg Ion Beam Therapy centre samples of charged secondary, prompt photons, $\beta^+$ production and forward fragmentation in PMMA target from primary $^{12}$C and $^4$He ion beams were collected. The charged secondary yields, energy spectra and emission profiles produced by $^{12}$C and $^4$He ion beams were measured at 90° and 60°. The obtained results confirm the feasibility of ion beam therapy range monitoring using $^{12}$C ion beams and suggest the possibility of range monitoring with $^4$He beams, in view of the studies documented in Traini et al (2017) and Battistoni et al (2017). The charged secondary production obtained with $^{16}$O beams is the subject of further analysis, and will be published in a dedicated manuscript. Prompt photon yields produced with $^4$He, $^{12}$C and $^{16}$O beams have been reported in Mattei et al (2017b). Forward fragmentation studies with $^4$He beam have been reported in Marafini et al (2017).

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