Secondary radiation measurements for particle therapy applications: prompt photons produced by $^4\text{He}$, $^{12}\text{C}$ and $^{16}\text{O}$ ion beams in a PMMA target

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Abstract
Charged particle beams are used in particle therapy (PT) to treat oncological patients due to their selective dose deposition in tissues with respect to the photons and electrons used in conventional radiotherapy. Heavy ($Z > 1$) PT beams can additionally be exploited for their high biological effectiveness in killing cancer cells. Nowadays, protons and carbon ions are used in PT clinical routines. Recently, interest in the potential application of helium and oxygen beams has been growing. With respect to protons, such beams are characterized by their reduced multiple scattering inside the body, increased linear energy transfer, relative biological effectiveness and oxygen enhancement ratio.

The precision of PT demands online dose monitoring techniques, crucial to improving the quality assurance of any treatment: possible patient mis-positioning
and biological tissue changes with respect to the planning CT scan could negatively affect the outcome of the therapy. The beam range confined in the irradiated target can be monitored thanks to the neutral or charged secondary radiation emitted by the interactions of hadron beams with matter. Among these secondary products, prompt photons are produced by nuclear de-excitation processes, and at present, different dose monitoring and beam range verification techniques based on prompt-γ detection are being proposed. It is hence of importance to perform γ yield measurement in therapeutic-like conditions.

In this paper we report on the yields of prompt photons produced by the interaction of helium, carbon and oxygen ion beams with a poly-methyl methacrylate (PMMA) beam stopping target. The measurements were performed at the Heidelberg Ion-Beam Therapy Center (HIT) with beams of different energies. An LYSO scintillator, placed at 60° and 90° with respect to the beam direction, was used as the photon detector. The obtained γ yields for the carbon ion beams are compared with results from the literature, while no other results from helium and oxygen beams have been published yet. A discussion on the expected resolution of a slit camera detector is presented, demonstrating the feasibility of a prompt-γ-based monitoring technique for PT treatments using helium, carbon and oxygen ion beams.

Keywords: prompt photons, online range monitoring, particle therapy, helium ions, oxygen ions, carbon ions

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

Introduction

Particle therapy (PT) exploits the characteristic energy release of charged particles in matter, mainly protons and carbon ions, in the irradiation of tumor volumes, trying to spare the surrounding healthy tissues as much as possible. In comparison to the most advanced photon radiotherapy technique, protons and carbon ions display the advantageous feature of having a high linear energy transfer (LET) and increased relative biological effectiveness (RBE), which make these particles particularly favourable in treating radio-resistant tumors (Loeffler and Durante 2013). Beside protons and carbon ions, helium and oxygen ion beams are currently being investigated as PT candidates (Tommasino et al 2015). Helium ions suffer less lateral multiple scattering with consequent reduced beam broadening with respect to protons, providing a good solution in the irradiation of radio-resistant tumors when low beam fragmentation is required (Fuchs et al 2014, Durante and Paganetti 2016, Krämer et al 2016). Oxygen ions could be advantageous when increased efficiency in treating radio-resistant tumors is needed due to their higher LET, RBE and oxygen enhancement ratio (OER) with respect to protons, carbon and helium (Kurz et al 2012).

The high spatial selectivity of PT makes this technique particularly sensitive to possible patient mis-positioning and anatomical variations, requiring the development of an online beam range monitor. This should be able to provide feedback on dose deposition spatial distribution during treatment in order to improve its quality and efficacy: the lack of precise online monitoring is one of the key issues to be addressed in supporting the diffusion of PT therapies in clinical centers. Beam range monitoring takes advantage of the secondary radiation produced by the interactions of the beam with the target nuclei along the path inside the target
volume: the beam is stopped inside the patient and the secondaries escaping from the body can be detected, their emission profile reconstructed and used to monitor the beam dose deposition and range. So far, the most established PT beam monitoring technique is based on the detection of back-to-back photons produced by the annihilation positrons coming from $\beta^+\gamma$ emitters (PET photons) using the positron emission tomography (PET) technique. Nevertheless, the signal level is lower in comparison with the PET signals known from clinical diagnostics, and at present such a technique is used off-line, after patient irradiation, aiming for further investigation methods (Parodi et al 2008).

Technology capable of online PET detection (Pawelke et al 1997, Parodi et al 2002, Fiedler et al 2008, Priegnitz et al 2008) is currently under development (Attanasi et al 2009, Vecchio et al 2009, Marafini et al 2015, Pennazio et al 2015). The characterization of the secondary radiation produced by $p$ and $^{12}$C beams of therapeutic energy has been the subject of an intensive experimental campaign in the recent past: the production of PET photons (Agodi et al 2012c, Enghardt et al 2004), light-charged fragments (Agodi et al 2012a, Henriquet et al 2012, Gwosch et al 2013, Piersanti et al 2014) and prompt photons has been the main object of this contribution, and has been studied in different experimental conditions (Kraan 2015). In particular, prompt-$\gamma$ production has recently been investigated by several experiments performed using $p$ and $^{12}$C beams of several energies: 73 MeV u$^{-1}$ (Testa et al 2008, 2009), 80 MeV u$^{-1}$ (Agodi et al 2012b, 2013), 220 MeV u$^{-1}$ (Mattei et al 2015), 95 MeV u$^{-1}$, 300 MeV u$^{-1}$ and 310 MeV u$^{-1}$ (Testa et al 2010, Pinto et al 2015). The prompt-$\gamma$ yield estimation is of particular importance since it strongly affects the achievable resolution in the evaluation of the hadron beam range. The main interests in using this kind of secondary radiation for monitoring purposes are related to its large abundance and the high precision achievable in emission point reconstruction in the absence of multiple scattering interactions.

In this paper we present the results of prompt photon production measurements performed using $^4$He, $^{12}$C and $^{16}$O beams, available at the Heidelberg Ion-Beam Therapy Center (HIT, Heidelberg, Germany), interacting with a beam-stopping PMMA target.

The experimental setup used for data acquisition is described in detail in section 1, while the results obtained with the LYSO detector at 60° and 90° with respect to the beam direction are discussed in section 2 and compared with the results available from the literature. The discussion of the measured fluxes in the context of monitoring applications can be found in section 3, taking the IBA knife edge slit camera as a reference detector for prompt gamma monitoring. Particular care has been made to quantify the impact of the collectable statistics of prompt photons emitted in particle therapy with heavy ion clinical-like scenarios on the precision achievable in dose deposition monitoring.

The experimental apparatus did not allow the prompt photon production position to be measured, and hence a disentangling of the photon production induced by the primary incoming radiation and of the secondary photons produced after the Bragg peak region was not possible. The implications for prompt photon monitoring are detailed in section 3.

1. Experimental setup

The experiment was performed at HIT where different ion species of several energies were used to irradiate a poly-methyl methacrylate (PMMA) target to study the prompt-$\gamma$ radiation emitted from the interactions of the beam projectiles with the target nuclei.

Figure 1 shows the experimental setup, which is part of a more extended geometry meant to measure not only prompt photon radiation, but also secondary charged particles, PET photons and forward emitted heavy fragments.
The origin of the reference frame is marked by a black spot inside the PMMA target. The beam, coming from the left along the $z$-axis, is illustrated with an arrow. To detect the incoming primary particles, a plastic scintillator (EJ200) 2 mm thick (Start Counter, SC) was placed $\sim 30$ cm upstream of the PMMA. The SC was read by two photomultiplier tubes (PMTs), Hamamatsu H6524, each one giving a recorded signal (SC1, SC2). The SC, used as a trigger detector, provided the number of impinging ions and the reference time for the time of flight (ToF) measurements.

The PMMA target dimensions are $(5.00 \times 5.00 \times t_{\text{PMMA}})$ cm$^3$, where $t_{\text{PMMA}}$ is the PMMA thickness that depends on the penetration depth of the primary beam and the experimental setup configuration used during data acquisition (see table 1). The uncertainty on $t_{\text{PMMA}}$ is 0.01 cm. For the data collection of the $^4$He and $^{16}$O ions, in order to keep the Bragg peak (BP) position fixed for all the beam energies, the size of the PMMA was changed according to the energy and range (BP depth) of each beam. For carbon ion data acquisition, the PMMA thickness was fixed at 10.00 cm regardless of the incoming beam energy, still ensuring that the beam stops within the PMMA.

A long thin scintillator (LTS) $(0.2 \times 5.0 \times 17.0)$ cm$^3$, read by an H10580 PMT, was placed on the PMMA lateral face in order to identify and study the secondary charged particles. A 21 cm long drift chamber (DCH) was mechanically aligned with the reference frame origin and placed at a distance of $\sim 60$ cm from the centre of the PMMA. The DCH, described in detail in Abou-Haidar et al. (2012), Agodi et al. (2012a) and Piersanti et al. (2014), was used to identify and reject the background from the low-energy charged particles (see section 2).

Prompt photons were detected by a $2 \times 2$ matrix of scintillating lutetium yttrium orthosilicate (LYSO) crystals, $(1.5 \times 1.5 \times 12.0)$ cm$^3$ each, described in detail in Agodi et al. (2012b). The detector was placed $\sim 2$ cm behind the DCH exit face and was mechanically aligned with the reference frame origin. In order to discriminate the LYSO signal from the LYSO intrinsic
background, the PMT threshold was set corresponding to a calibrated LYSO deposited energy of \( \sim 1 \text{ MeV} \).

The energy calibration of the LYSO scintillator was performed with the final data acquisition setup at HIT using a radioactive source of \(^{60}\text{Co}\). The data collected was used to provide the reference point needed for the implementation of a former calibration of the very same crystal that was performed in the range of interest for prompt photon emission studies, with a different experimental setup, and is documented in detail in a separate manuscript (Bellini et al. 2014). A linear calibration curve, up to \( \sim 10 \text{ MeV} \), is assumed following the results obtained in the extended calibration energy range study presented in Bellini et al. (2014). The ToF slewing effect induced by the front-end electronics fixed voltage threshold was taken into account following the procedure described in Agodi et al. (2012b) and Agodi et al. (2013).

The DCH and LYSO detectors were attached to the same movable aluminum arm. This arm can be placed at different angles with respect to the beam direction (\( \theta \)), i.e. 60° and 90°, in order to measure the angular dependence of the prompt-\( \gamma \) emission. The total distance of the LYSO from the PMMA center was \( 82.00 \pm 0.1 \text{ cm} \) in the 90° setup and \( 86.50 \pm 0.1 \text{ cm} \) in the 60° setup. Both detectors were pointing towards the expected position of the BP for the \(^{4}\text{He}\) and \(^{16}\text{O}\) beam studies, while during the \(^{12}\text{C}\) beam studies, the arm axis was aligned with the BP position only in the most energetic case (220 MeV \( \text{u}^{-1} \)). Hence, \(^{12}\text{C}\) runs taken at lower energies have a BP that is shifted on the left (lower \( z \) values), as can be computed from the range values reported in table 1.

Figure 1 also shows the positioning of two LYSO pixellated \( \gamma \)-PET detectors (PETs and \( \text{PET}_{n} \)) used to monitor the production of \( \beta^{+} \) emitters\(^9\) during PMMA irradiation. The PET trigger line requires the coincidence in time of the signals of the LYSO detectors, and is independent of the SC signals in order to allow the measurements of the \( \beta^{+} \)-induced activity to be made, including occasions when the beam was not impinging on the target.

The \( \gamma \)-PET detectors were included in the simulation of the experimental apparatus and used to provide an independent check of the number of incoming ions, as described in section 2.3.

Table 1 summarizes the measured setup configurations relative to the collected data sample. For each ion species, the beam energy (Energy) and spot size (\( B_{\text{FWHM}} \)) as the full width at half maximum (FWHM) from the HIT libraries are reported (later in the text, the

\(^9\)The obtained results, as well as the experimental methods, will be the subject of a dedicated manuscript currently in preparation, and will hence be documented in detail elsewhere.

| Ion   | Energy (MeV \( \text{u}^{-1} \)) | \( B_{\text{FWHM}} \) (mm) | Range (cm) | \( t_{\text{PMMA}} \) (cm) | \( \theta \) |
|-------|--------------------------------|----------------------------|------------|-----------------|-----------|
| \(^{12}\text{C}\) | 120.45                       | 7.9                        | 2.88       | 10.00           | 90°       |
|       | 159.99                       | 6.2                        | 4.83       |                 |           |
|       | 180.89                       | 5.5                        | 6.03       |                 |           |
|       | 219.79                       | 4.7                        | 8.33       |                 |           |
| \(^{4}\text{He}\) | 102.34                       | 9.3                        | 6.68       | 7.65            | 60°       |
|       | 124.78                       | 7.8                        | 9.68       | 10.00           | 90°–60°   |
|       | 144.63                       | 6.9                        | 12.63      | 12.65           |           |
| \(^{16}\text{O}\) | 209.63                       | 4.6                        | 5.78       | 7.65            |           |
|       | 259.55                       | 3.9                        | 8.38       | 10.00           | 90°–60°   |
|       | 300.13                       | 3.6                        | 10.68      | 12.65           |           |
beam energies will be approximate values). The relative error on the HIT beam energies is of \(1.5 \cdot 10^{-3}\) (Parodi et al. 2012). The beam range in the PMMA, defined as the BP position depth inside the target (Range), was computed using a FLUKA Monte Carlo (MC) simulation (Ferrari et al. 2005, Boehlen et al. 2014, Battistoni et al. 2015). The error on the reported Range values is 0.05 cm, determined from the simulated Bragg curves of each beam impinging on a PMMA target (density: 1.19 g cm\(^{-3}\); ionization potential: 74 eV). For each data acquisition, the PMMA thickness (\(t_{\text{PMMA}}\)) and the DCH/LSYO angular configuration (\(\theta\)) are also listed.

The data acquisition (DAQ) trigger was provided by the time coincidence of the logic OR of the SC signals (SC1 or SC2) with the LYSO signal. This choice was driven by the need to optimize the data sample collection efficiency and to allow for a measurement of the SC detector efficiency. It should be noted that the data analysis performed for prompt photon study requires the AND of the SC1 and SC2 signals in all the steps, to minimize the contribution of random electronic noise to the measurement of the number of incoming ions.

All electronic signals were read out by a VME system (CAEN V2718 VME-PCI bridge) interfaced with a PC for the DAQ. The time and charge information for the signals of all the detectors were acquired using a 19-bit TDC multi-hit (CAEN V1190B, time resolution of \(\sim 100\) ps), and a 12-bit QDC (CAEN V792N, resolution of \(\sim 0.1\) pC). The digitization of the time information was accomplished by means of a discrimination system in which the digital output signals had a 100 nm width. The impact of this choice in the counting of events with multiple ions impinging on the SC is discussed in detail below (section 1.1).

The number of impinging ions was counted by means of a VME scaler (CAEN V560N), using the logic AND of the SC signals (SC1 and SC2, defined as SCAND). The VME scaler is capable of sustaining an incoming signal rate up to 100 MHz.

### 1.1. Beam description

The ion beams provided by the HIT facility are accelerated using a synchrotron. The incoming beam rate, kept under the 10 MHz limit set by the SC signal discrimination time used for the ToF measurements, ranged from \(\sim 300\) kHz up to \(\sim 3\) MHz, depending on the ion beam species. Such a rate was heavily reduced with respect to the therapeutic rates in order to allow the experimental data acquisition.

The beam time profile (Beam rate) is shown for \(^4\)He (left), \(^{12}\)C (center) and \(^{16}\)O (right) data samples in figure 2 as a function of the elapsed data acquisition time (elapsed time). The spill structure of the beam is clearly visible.
The fine structure of the beam, instead, was measured by means of the multi-hit TDC in a 2 μs window around the trigger time, and it is shown in black dots in figure 3 (left) for events collected using the 4He beam of 144.63 MeV. Similar spectra were also obtained for the 12C and 16O beams.

The fine structure of the beam was measured using the data collected for the different acquisition runs, in a time window far from the trigger, e.g. for the 4He events in the 200–800 nm window. Such data was used to build a probability density function describing the beam shape and used to perform an MC simulation in order to account for the inefficiencies, in the detection of multiple ion events, introduced by the fixed time window set by the discriminators used to process the analogic signals from the SC detector. The ion rate used to generate the events in the MC simulation was tuned to optimize the agreement between the MC (shown as histograms in blue continuous lines) and the measured distributions of the data (shown as black dots), as in figure 3. A remarkable agreement is observed, allowing the reliable measurement of discrimination-window-induced inefficiencies.

The difference in the arrival time of multiple ions is shown in figure 3 (right), in black dots for the collected data, and shows the inefficiency introduced for ions impinging on the SC with a time distance that is smaller than 100 nm. The red dashed line in figure 3 (right) shows the difference in the arrival time of all the simulated ions, while the blue continuous line shows the time difference after a 100 nm discrimination window is taken into account. The systematic uncertainties relating to the inefficiency measurement are discussed in section 2.2.

The beam spot size $B_{\text{FWHM}}$, as reported in table 1, is inversely proportional to the beam energy for each ion species. It ranges between 6.9–9.3 mm for 4He beams, 4.7–7.9 mm for 12C beams and 3.6–4.6 mm for 16O beams.

The maximum trigger rate was 6 kHz, which was the limit set by the DAQ dead time. The trigger lines were set up for the different measurements pointed out at the beginning of section 1: forward fragmentation studies, charged particles and prompt photon production at large angles and $\beta^+$ emitter production. The trigger line used for the prompt photon studies had a mean rate in the 300 Hz–2 kHz range, depending on the beam conditions, and contributed to 5%–30% of the total trigger rate.
2. Prompt photon yield

The yield of prompt photons produced by the ion beam projectile interaction with the PMMA target, normalized to the total solid angle and integrated over the full target length, was computed according to the following equation:

\[
\Phi_\gamma (\text{sr}^{-1}) = \frac{1}{4\pi \varepsilon_{\text{TOT}} \varepsilon_{\text{DT}}} \times \frac{N_\gamma}{N_{\text{ion}}}
\]

where \(N_\gamma\) is the number of prompt photons measured by the LYSO detector in the (2–10) MeV energy range, \(N_{\text{ion}}\) is the total number of primary ions impinging on the PMMA target, \(\varepsilon_{\text{TOT}}\) is the total detector efficiency (including the detector and geometrical contributions) and \(\varepsilon_{\text{DT}}\) is the data acquisition dead time efficiency.

Although the analysis was performed starting from 1 MeV, the lower limit in the energy range for the yield evaluation was conservatively set to 2 MeV. Above this threshold, the background contribution, mainly due to the intrinsic radioactivity of LYSO, electronic noise and neutrons, becomes negligible. The upper energy limit in the yield evaluation was set to 10 MeV: above this energy level, we expected no significant de-excitation gamma lines from the carbon and oxygen nuclei or their residues produced by nuclear reactions (National Nuclear Data Center, www.nndc.bnl.gov).

The prompt photon number \(N_\gamma\) was evaluated starting from the two-dimensional distribution of the deposited energy in the crystal \(E_{\text{LYSO}}\) as a function of the time of flight (ToF) of the secondaries interacting in the LYSO (see figure 4).

The ToF is defined as the time difference between the signal detected in the LYSO and the signal detected in the SC (SCAND) induced by a traversing ion \((t_{\text{LYSO}} - t_{\text{SCAND}})\). In this definition of ToF, the time slewing effect is corrected following the same procedure described in Agodi et al (2012b).

Figure 4 shows, as an example, the \(E_{\text{LYSO}}\) versus ToF distribution used to select the prompt-\(\gamma\) signal for the events taken using \(^4\text{He}\) (left) and \(^{16}\text{O}\) (right) ions as projectiles. The distributions were obtained combining the data obtained in the different energy configurations and collected at 90 degrees. A scaling factor was applied to both histograms in order to normalize the distributions to the same statistics (10⁷ events). The horizontal low energy band visible in both plots \((E_{\text{LYSO}} < 1.5\ \text{MeV})\) is related to the LYSO intrinsic noise, while the diffused cloud is associated with neutrons and a ToF that is almost uncorrelated to the SC signal. The vertical band at 0 nm is relative to the prompt photon signal.
$N_γ$ was computed from the reduced ToF ($\text{ToF}/\sigma_{\text{ToF}}$) distributions, selected in the $[-10,10]$ interval and sampled in the $E_{\text{LYSO}}$ bins of $\sim$0.2 MeV. The $\sigma_{\text{ToF}}$ values were extracted from the time slewing correction procedure, where the ToF distributions sampled in the $E_{\text{LYSO}}$ bins were modeled with a Gaussian function (more details can be found in Agodi et al. (2012b)). The number of prompt photons was extracted from an unbinned maximum likelihood fit, performed using the RooFit toolkit from ROOT (Verkerke and Kirkby 2003), to the reduced time distribution for each energy bin. Figure 5 shows two examples of reduced time distribution in lower (1.4 MeV < $E_{\text{LYSO}}$ < 1.6 MeV, shown on the left) and higher (4.6 MeV < $E_{\text{LYSO}}$ < 4.8 MeV, shown on the right) energy bins for a 145 MeV/u helium ion beam run with the LYSO detector placed at $\theta = 90^\circ$.

The total fit function (solid line) is superimposed on the data spectrum: the background, mainly due to neutrons, is described by a crystal ball (Skwarnicki 1986) shape (dotted line), while the signal is modeled using a Gaussian probability density function (PDF, dashed line). The crystal ball function well represents the neutron background, especially in the low energy range ($E_{\text{LYSO}} \sim 2$ MeV). The background coming from the low-energy charged particles was reduced by requiring that the number of hits detected in the drift chamber ($N_{\text{hit}}$) is less than three (the average number of hits detected for a charged particle traversing the DCH is 12). As a cross-check for the charged particle background relevance in the final result, an LTS detector was used as an additional veto for the charged particles; the combined use of DCH and LTS did not result in a sensible change of the yields, and hence we did not explicitly include the LTS charged particle veto in the final analysis.

The dead time (DT) efficiency $\varepsilon_{\text{DT}}$ was evaluated using the VME scaler, in which all the generated trigger signals ($N_{\text{TrTot}}$) and the trigger signals acquired by the DAQ system ($N_{\text{TrAcq}}$), were counted. The DT efficiency, defined as $\varepsilon_{\text{DT}} = N_{\text{TrAcq}}/N_{\text{TrTot}}$ varied from 60%–90%, depending on the beam rate. The average values of $\varepsilon_{\text{DT}}$ for the different data acquisition conditions (ion species, beam energies and angular configurations) were used to compute the integrated yields using equation (1).

The total number of primary ions impinging on the PMMA target is defined as $N_{\text{ion}} = N_{\text{ion}}^{\text{raw}} \times \varepsilon_{\text{corr}}$ where $N_{\text{ion}}^{\text{raw}}$ is the number of primary ions computed counting the number of SCAND signals over the threshold as described in section 1.
The obtained counts have to be corrected by $\text{corr}_{\text{ion}}$, a correction factor that takes into account the inefficiency due to the 100 nm dead time introduced by the width of the SC discriminated signals.

As discussed in section 1.1, and shown in figure 3 (right), this correction was evaluated as an average fraction of lost ions using a dedicated MC simulation tuned in order to reproduce the temporal beam structure of each data set that was acquired. $\text{corr}_{\text{ion}}$ was measured as the ratio of all the events impinging on the SC, without applying any cut (as shown in figure 3 right, red dashed histogram), to the number of events in which the arrival time difference of multiple ions was greater than 100 nm (as shown in figure 3 right, blue solid histogram). The measured $\text{corr}_{\text{ion}}$ values, computed for each data set to take into account the different beam rates, are in the range [1.0, 1.5].

2.1. MC simulation

The detector and geometrical efficiencies ($\varepsilon_{\text{TOT}}$) were computed using an MC simulation based on the FLUKA code, that implemented all the experimental configurations (the beam characteristics and experimental setup as described in section 1 by table 1 and shown in figure 1).

The total efficiency $\varepsilon_{\text{TOT}}$ was defined as the ratio of $N_{\gamma}^{\text{meas}}$ to $N_{\gamma}^{\text{gen}}$, where $N_{\gamma}^{\text{meas}}$ is the total number of prompt photons measured by the LYSO detector, after having applied the same signal selections performed in the experimental data analysis, and $N_{\gamma}^{\text{gen}}$ is the total number of prompt photons produced with an energy of $>2$ MeV by the ion beam interacting with the PMMA target. The computed $\varepsilon_{\text{TOT}}$ ranges from $6.6 \cdot 10^{-5}$ up to $8.6 \cdot 10^{-5}$, depending on the different experimental setup conditions.

The computed efficiency depends mainly on the modeling of the prompt photon transport from the production point inside the PMMA target up to the LYSO detector. To evaluate the impact of the dependence of the measured efficiency on the nuclear models used in FLUKA to generate the prompt photon emission spectrum, an ad hoc MC simulation was set up. Photons were generated assuming a flat energy spectrum (between 1 and 15 MeV) as well as a simple spatial distribution, flat along $z$ extending over the full PMMA length, and the Gaussian in the transversal plane with the FWHM equal to the known beam transversal dimension (see table 1).

The efficiency values obtained with both simulations (the one relying on the FLUKA nuclear models and the one in which a flat distribution was assumed) were compatible within the uncertainties, proving that the details of the production energy and position emission spectrum have a negligible impact on the efficiency averaged over the energy interval under study (2–10 MeV) for the described experimental setup (see section 1). Care was taken in order to ensure that significant statistics were collected for all the relevant energies and emission positions, allowing a measurement in which the dominant contribution to the uncertainty was systematic.

As the interactions of the photons in the 1–20 MeV energy range with matter are known to be very well reproduced in FLUKA, particular care was made in setting up a simulation in which all the detector and experimental apparatus parts were properly included and positioned, especially those traversed by the photons in their path towards the LYSO detector. The uncertainty related to the geometrical survey measurements and detector description details on the efficiency measurements are discussed in the systematic uncertainty section (section 2.3).

2.2. Results

The production yields of prompt photons ($\Phi_{\gamma}$) produced by $^4$He, $^{12}$C and $^{16}$O ion beams, computed according to equation (1), measured with the detector in the angular configuration at 90° and 60°, with a deposited energy $E > 2$ MeV, integrated over the full target size and averaged
in a full $4\pi$ solid angle, for the different ion beam energies are listed in table 2. For each ion species, $\Phi_\gamma$ increases with increasing energy, both at $90^\circ$ and $60^\circ$, while no angular dependence is in evidence in the integrated production yield. Furthermore, as a first approximation, universal behavior as a function of the primary energy exists independently of the nuclear species, as shown in figure 6.

It should be noted that the results presented in this manuscript are related to the total integrated production of prompt photons occurring as a direct consequence of the interactions of primary ions with a target medium (primary component) that is limited up to the BP region and of other indirect nuclear processes (secondary component) that can lead to significant prompt photon production even after the BP region (Pinto et al 2015). While the data collected with the most energetic $^{12}$C beam and the $^4$He and $^{16}$O beams had a BP position that was close (1 cm or less) to the exit (rear) PMMA face, and hence the secondary production of photons can be considered as similar and subdominant in all cases, particular care has to be taken when comparing the low-energy carbon yields with results obtained in other experimental conditions. However, the nice agreement of the yields shown in figure 6 for the $^{12}$C beam at 120 MeV u$^{-1}$ and the measurement presented in Pinto et al (2015) ($^{12}$C at 95 MeV u$^{-1}$) and in Agodi et al (2013) ($^{12}$C at 80 MeV u$^{-1}$) obtained in completely different experimental conditions suggests that the secondary component, while certainly present, is not dominant for these beam or (low) energy pair conditions.

The results from carbon ion beams were compared with other results from the literature. As reported in Mattei et al (2015), the prompt photon production yield obtained from a 220 MeV u$^{-1}$ $^{12}$C beam impinging on a PMMA target, integrated over the full target size ($5 \times 5 \times 20$ cm$^3$) and averaged in a full $4\pi$ solid angle, measured with a LYSO detector at the GSI (Darmstadt, Germany) facility is $\Phi_\gamma(\text{220 MeV/u, } E > 2 \text{ MeV } @ 90^\circ) = (6.3 \pm 0.2_{\text{stat}} \pm 2.1_{\text{syst}}) \times 10^{-3}$ sr$^{-1}$. This experimental result is less than 3 standard deviations away from the correspondent HIT yield $\Phi$, shown in table 2.
The production yield was also measured at GSI using a BaF2 detector (Vanstalle et al. 2016) obtaining a value of $\Phi_\gamma \pm \sigma_{\text{stat}} \pm \sigma_{\text{sys}} = (10.6 \pm 0.1_{\text{stat}} \pm 1.1_{\text{sys}}) \times 10^{-3} \text{ sr}^{-1}$, in agreement within 1 standard deviation with the corresponding value shown in table 2.

The measured yields were also compared with what is presented in Pinto et al. (2015), where the prompt-$\gamma$ absolute yield produced by a $^{95}\text{MeV u}^{-1}\ ^{12}\text{C}$ beam interacting with a PMMA target, with an energy threshold of $2 \text{ MeV}$, averaged over the full beam range, was reported to be $(1.74 \pm 0.09_{\text{stat}} \pm 0.50_{\text{sys}}) \times 10^{-4} \text{ mm}^{-1} \text{ sr}^{-1}$. In order to relate the integrated yield produced by the $^{120}\text{MeV u}^{-1}\ ^{12}\text{C}$ carbon ion beam shown in table 2 with Pinto’s result, we used an estimate of the full projected range for our beam of 30.86 mm, as estimated by SRIM 2013. With this assumption, the normalized rate becomes $\Phi_\gamma(^{12}\text{C} \ 120 \text{ MeV u}^{-1} \ 90^\circ) = (1.48 \pm 0.03_{\text{stat}} \pm 0.09_{\text{sys}}) \times 10^{-4} \text{ mm}^{-1} \text{ sr}^{-1}$, in agreement with what was measured in Pinto et al. (2015).

### Table 2. The production yields ($\Phi_\gamma$) of prompt photons, computed according to equation (1), measured with the detector in the angular configuration at $90^\circ$ and $60^\circ$, with a deposited energy threshold $E > 2 \text{ MeV}$, integrated over the full target size and averaged in a full $4\pi$ solid angle for the different ion beam energies. The statistical ($\sigma_{\text{stat}}$) and systematic ($\sigma_{\text{sys}}$) uncertainties are shown as well.

| $\theta$ | Ion   | Energy (MeV u$^{-1}$) | $\Phi_\gamma \pm \sigma_{\text{stat}} \pm \sigma_{\text{sys}} (10^{-3} \text{ sr}^{-1})$ |
|---------|-------|-----------------------|----------------------------------------------------------------------------------|
| 90$^\circ$ | $^4\text{He}$ | 125 | 5.34 ± 0.06 ± 0.23 |
|         |       | 145 | 6.53 ± 0.07 ± 0.27 |
|         | $^{12}\text{C}$ | 120 | 4.56 ± 0.09 ± 0.28 |
|         |       | 160 | 7.59 ± 0.13 ± 0.35 |
|         | $^{16}\text{O}$ | 180 | 9.65 ± 0.18 ± 0.53 |
|         |       | 220 | 12.19 ± 0.24 ± 1.11 |
|         |       | 260 | 16.83 ± 0.20 ± 0.65 |
|         |       | 300 | 22.10 ± 0.15 ± 0.81 |
| 60$^\circ$ | $^4\text{He}$ | 102 | 3.70 ± 0.08 ± 0.11 |
|         |       | 125 | 4.67 ± 0.07 ± 0.18 |
|         | $^{16}\text{O}$ | 145 | 6.40 ± 0.08 ± 0.27 |
|         |       | 210 | 12.44 ± 0.13 ± 0.51 |
|         |       | 260 | 17.04 ± 0.19 ± 0.69 |
|         |       | 300 | 21.32 ± 0.19 ± 1.09 |

2.3. Systematic uncertainties

Several sources contribute to the total systematic uncertainty ($\sigma_{\text{sys}}$) of the integrated absolute yield.

The $N_\gamma$ value was computed using an unbinned maximum likelihood fit of the reduced ToF distributions. In order to evaluate the systematics relating to the signal and background fit models, a different approach to the counting of signal events has been used. The background contribution in the signal region (ToF/$\sigma_{\text{ToF}} \in [-3, 3]$) was extrapolated from the unbinned fit of the side bands (SB) of the ToF/$\sigma_{\text{ToF}}$ spectra (ToF/$\sigma_{\text{ToF}} \in [-10, -3) \cup (3, 10]$). Therefore, the signal events were computed as the total number of events in the signal region after the subtraction of the background, as obtained from the SB extrapolation. The difference between
the values obtained for $N$, from the SB subtraction method and the full fit analysis, significant only for the cases of $^{12}$C beams, was used as an estimate of the systematic source from the $N$, evaluation and added in quadrature to $\sigma_{\text{sys}}$ in the computation of the $^{12}$C $\Phi$. The relative contribution of the $N$, systematics to the total uncertainty varies from $\sim 2\%$ up to $\sim 8\%$.

The measured total number of primaries $N_{\text{raw}}^{\text{ion}}$ impinging on the PMMA target was computed using the number of SCAND signals ($N_{\text{SCAND}}$). In order to evaluate the systematic uncertainty due to the $N_{\text{SCAND}}$ evaluation, an independent measurement of $N_{\text{raw}}^{\text{ion}}$ was necessary and was provided by the trigger line of the PET photon measurement. The PET trigger is not related to the SC detector, but it is related to the true number of ions interacting in the target. The ratio of the number of PET triggers ($N_{\text{PET}}$) to the SCAND signals was therefore studied and found to be constant within the statistical uncertainty of $N_{\text{PET}}$. Since this is the intrinsic limit of the systematic error on $N_{\text{raw}}^{\text{ion}}$, the statistical fluctuation of $N_{\text{PET}}$ was assigned as the systematic uncertainty to the estimated number of primaries. The relative contribution to the total uncertainty from this source ranges between $\sim 3\%$–$6\%$.

As already discussed beforehand, the $N_{\text{raw}}^{\text{ion}}$ measurement was corrected taking into account the inefficiency in the selection of multiple ions impinging on the SC at times shorter than 100 ns using the correction factor $\text{corr}_{\text{ion}}$. The details of the MC simulation that was set up to account for this inefficiency are given in section 1.1. The systematic uncertainty due to this MC correction was evaluated by performing a dedicated study in which the beam rate and the spill shape of the MC model were varied within the uncertainties. The beam rate was changed from the value obtained by the data/MC agreement tuning to the mean value measured in the data, while the beam shape, obtained from a fit to the data sample, was varied to take into account the uncertainties of the fit parameters and fit range. The relative contribution to the total uncertainty from this source varies from $\sim 1\%$ up to $\sim 5\%$.

The systematic uncertainty of the total efficiency was computed by using the FLUKA MC simulation and varying the simulated set up geometry, in order to account for the uncertainty of the relative positions of the different detectors as well as of the PMMA target and beam size. The overall contribution to the total systematic uncertainty was found to be negligible in all cases. The $\epsilon_{\text{TOT}}$ evaluation was also performed using an ad hoc MC simulation, described in section 2.1, to test the dependence of the obtained average values on the underlying nuclear models implemented in FLUKA to generate the position and energy spectrum of the photons. The efficiency values obtained using the ad hoc simulation were found to be consistent with the values obtained by the fully detailed FLUKA-based simulation, and thus no systematic uncertainty was assigned to this effect.

The systematic error due to the maximum energy cut (10 MeV) in the $N$, integral computation was checked against the MC simulation: the fraction of photons above this threshold ($f_{\text{lost}}$) is of the order of $2\%$ for the helium and carbon cases and for the oxygen beam of 210 MeV at $90^\circ$. For the other oxygen configurations $f_{\text{lost}}$ is $\sim 1\%$ and was added to $\sigma_{\text{sys}}$.

Another possible systematic source of the yield evaluation is the 2 MeV lower limit of the energy range for the $N$, integral computation, due to possible energy shifts depending on the LYSO calibration curve. The systematic uncertainty of the LYSO calibration has therefore been computed varying the calibration parameters of $3\sigma$ around their mean values and taking into account their correlation coefficient: it is found to be negligible.

The systematic contribution coming from the background rejection of low-energy charged particles using the $N_{\text{hit}} < 3$ selection was studied. Exploiting the MC simulation that reproduces the DCH number of hit data distribution, the raw $N$, integral was computed asking for $N_{\text{hit}} < 2$ and $N_{\text{hit}} < 4$, and no significant variation was observed.
3. Prompt-\(\gamma\) monitoring applications

The research and development of particle therapy online monitoring devices relies on the experimental knowledge of the abundance and energy spectrum of secondary radiation produced by the incoming beam interaction with the patient body. As stated in the previous sections, prompt photon radiation can be used to monitor the beam range inside the target during PT treatment. The resolution achievable in the measured beam range depends on the production yield of the prompt-\(\gamma\)s, their emission energy and the technology that is used to detect them.

In order to estimate the resolution achievable in the beam range using the prompt photons produced by the interaction of \(^{4}\text{He}\), \(^{12}\text{C}\) and \(^{16}\text{O}\) ion beams with a PMMA target, we used the results published in Smeets \textit{et al} (2012), where the performances of a slit camera recently developed by the IBA are documented.

The results presented in Smeets \textit{et al} (2012) were obtained studying the prompt-\(\gamma\)s produced by the interactions of a \(160\text{ MeV}\) proton beam impinging on a PMMA target. Figure 32 in Smeets \textit{et al} (2012) shows the range estimation standard deviation as a function of the number of irradiated primary protons as measured by the IBA slit camera.

The use of a result obtained studying the interactions of a proton beam to assess the monitoring performances reachable in PT treatments with \(^{4}\text{He}\), \(^{12}\text{C}\) and \(^{16}\text{O}\) ion beams is possible, once the number of primary ions that have to be shot in order to deliver a given dose to a selected target volume (depth and dimensions fixed) is known.

Using a dedicated MC simulation it is possible to compute the number of primary ions in all the different configurations of ions (\(^{4}\text{He}\), \(^{12}\text{C}\) and \(^{16}\text{O}\)) and energies of interest. The produced prompt photons in a given slice, relative to the pencil beams that have the same energy and hence are used to treat the tumor at a given fixed depth, can then be computed using the results presented in this manuscript, and the detector performances (which are independent of the secondary radiation production source) can be properly assessed.

Two important implications of the proposed strategy must be clarified:

- The number of primary ions that need to be shot during real treatment at any target volume has a strong dependence on the details of the total tumor region under treatment. Besides the obvious dependence on the energy of the beam, for each slice under treatment the number of ions that have to be shot depends on the slice position within the total target volume, in order to account for the dose pile up, and also of the RBE weight applied to each voxel. The assumptions used to obtain the results presented in this manuscript are outlined below.

- The number of prompt photons that are emitted during the treatment is also dependent on the material that is present after the BP: a secondary emission can occur that is not directly related to the nuclear interactions of the primary beam particles with the target volume. The results obtained in this manuscript are related to the total prompt photon production, not having any experimental mean to disentangle the two different production mechanisms. Hence, the flux used to compute the final number of photons has a direct dependence on the experimental conditions used to obtain the results presented in table 2, as discussed in section 2.2.

The study documented in this manuscript refers to two distinct and well-defined treatment configurations, studied using a dedicated FLUKA MC simulation. The first one to be used as a reference (a) while the second one represents a real case scenario as described by Krämer \textit{et al} (2000) (b):
Table 3. The number of primary particles needed to deliver a physical dose of 1 Gy in a slice of $10 \times 10 \times 3 \text{ mm}^3$ centered on the BP position ($\sim 85$ mm depth) in a PMMA target as predicted by a FLUKA MC simulation. The corresponding prompt photon absolute yield is reported in the last column, computed using the measurements shown in table 2.

| Beam        | Number of primaries | Absolute yield ($\times 10^5$ counts sr$^{-1}$) |
|-------------|---------------------|-----------------------------------------------|
| $^4$He 125 MeV u$^{-1}$ | $1.9 \times 10^8$ | $(10.15 \pm 0.11_{\text{stat}} \pm 0.44_{\text{sys}})$ |
| $^{12}$C 220 MeV u$^{-1}$ | $4.4 \times 10^7$ | $(5.36 \pm 0.14_{\text{stat}} \pm 0.49_{\text{sys}})$ |
| $^{16}$O 260 MeV u$^{-1}$ | $2.4 \times 10^7$ | $(4.04 \pm 0.05_{\text{stat}} \pm 0.16_{\text{sys}})$ |

(a) 1 Gy dose homogeneously distributed in a slice of $10 \times 10 \times 3 \text{ mm}^3$ surface, 3 mm thickness along the beam direction, centered on the Bragg peak position at a depth in the PMMA of $\sim 85$ mm;
(b) 1 Gy dose delivered to a tumor of 120 cm$^3$, divided in 39 slices.

The conclusions relating to the number of prompt photons generated in well-defined scenarios are an indication of the expected number of produced photons in conditions that are, under some assumptions, not far from typical treatment conditions, but are not meant to be used as representative of the final performance attainable in generic PT treatments, as those will have to be assessed using dedicated full MC simulations.

In both cases, the number of primary $^4$He, $^{12}$C and $^{16}$O ions of a given energy needed to deliver the desired dose was evaluated, and in the $^{12}$C case is of the same order of magnitude as the number of ions used in real treatments performed at CNAO. The physical dose (1 Gy) was chosen as a reference considering that the RBE weighted dose is of the order of $\sim 2$ RBE-Gy and that in a PT treatment at CNAO, using two laterally opposed carbon-ion beams, a value of RBE-weighted dose of 70.4 RBE-Gy divided in 16 fractions of 4.4 RBE-Gy each was prescribed to a skull-base chordoma target volume ($\sim 2$ RBE-Gy for each beam) (Russo et al 2016). We thus used the 1 Gy value as representative of the total RBE weighted dose, averaged over the SOBP region, for a given PT with heavy ions. Such an assumption, and the related conclusions, can be modified and adapted to different total doses to account for different details of the treatment under study using a dedicated MC simulation. However, conclusions on the feasibility of prompt photon monitoring do not change, as they are related to the order of magnitude of the emitted photons.

The expected prompt photon absolute yields were estimated using the results reported in table 2, in the 90° angular configuration.

For the $a$ configuration, the number of primaries predicted by the MC simulation and the relative amount of prompt-$\gamma$s produced are reported in table 3. As previously outlined, Smeets et al (2012) quoted the standard deviation of the estimated beam range using the prompt photon radiation as a function of the number of 160 MeV primary protons irradiating a PMMA target. Hence, using the measurement of the prompt photon yield emitted by a 160 MeV proton beam reported in Pinto et al (2015), we computed the number of primary protons needed to produce the prompt-$\gamma$ absolute yields listed in the last column of table 3. For the $^4$He beam we obtained $\sim 4 \times 10^8$ primary protons, for $^{12}$C and $^{16}$O beams we obtained $\sim 2 \times 10^8$ protons, and hence, an expected standard deviation of the beam range estimation that is less than 2 mm.

These preliminary results can be used as a basis to discuss prompt photon applications in beam range monitoring in the scenario of a real treatment plan, described in the $b$ configuration. In Krämer et al (2000), a total number of $\sim 7 \times 10^8$ carbon ions is needed to deliver 1 Gy
of absorbed dose to a tumor of 120 cm³ divided in 39 slices. As an exercise, assuming that each energy slice is irradiated with \(2 \times 10^7\) \(^{12}\)C ions of 220 MeV u⁻¹, we computed an expected absolute prompt photon yield per slice that is \((2.44 \pm 0.05_{\text{stat}} \pm 0.22_{\text{sys}}) \times 10^5\) counts sr⁻¹. If 125 MeV u⁻¹ \(^{4}\)He and 260 MeV u⁻¹ \(^{16}\)O ion beams are considered, to deliver the same physical dose as \(2 \times 10^7\) \(^{12}\)C ions, a number of \(8.6 \times 10^7\) \(^{4}\)He and \(1.1 \times 10^7\) \(^{16}\)O is needed, producing a \(\gamma\) yield of \((4.59 \pm 0.05_{\text{stat}} \pm 0.20_{\text{sys}}) \times 10^5\) and \((1.85 \pm 0.02_{\text{stat}} \pm 0.07_{\text{sys}}) \times 10^5\) counts sr⁻¹ respectively. The expected resolutions when using a slit camera have been computed for the real case scenario, as done before for the \(a\) configuration: the number of equivalent 160 MeV primary protons needed to produce the predicted prompt-\(\gamma\) yields from \(^{4}\)He, \(^{12}\)C and \(^{16}\)O ions was estimated. The obtained relative expected standard deviation of the beam range estimation has values smaller than 3 mm for \(^{12}\)C and \(^{16}\)O and smaller than 2 mm for \(^{4}\)He.

It should be noted that physical doses larger than 1 Gy can be delivered in a typical treatment fraction, and hence our estimate of the achievable resolution in the beam range can be considered as conservative. Furthermore, we would like to point out that in hypofractionated treatments, the relevance of possible real-time monitoring will be particularly significant. Our results support the conclusion that monitoring techniques exploiting prompt photons are feasible in particle therapy, providing a resolution in the beam range matching the clinical requirements.

To evaluate the monitoring performances in real treatment cases, it is necessary to take into account all the patient/treatment specific characteristics, like the tumor volume, its location inside the body and the different tissues that have to be traversed by the beam. A systematic study of the impact on the prompt gamma monitoring performance of the target inhomogeneities will be performed in the future, testing different geometrical configurations and beam energies. Furthermore, a substantial contribution to predictions when considering real treatment scenarios can also be provided by the Monte Carlo simulations, progressively updated with experimental data measurements.

4. Conclusions

The prompt photon production of \(^{4}\)He, \(^{12}\)C and \(^{16}\)O beams interacting with a beam-stopping PMMA target was studied at the HIT Heidelberg facility with beam energies of interest for PT applications. The production yield measurements performed in this study using \(^{12}\)C ions beam are found to be in agreement with results obtained from other experiments.

The \(^{4}\)He and \(^{16}\)O beams, whose prompt-\(\gamma\) production is herein measured for the first time, are particularly relevant for future PT applications. The obtained results confirm that non-negligible prompt photon production occurs in the interactions of \(^{4}\)He and \(^{16}\)O beams of therapeutic energy with a PMMA target.

The measured yields were used to compute the expected resolution in the beam range of a typical treatment scenario, assuming the performance of the IBA slit camera documented in Smeets et al (2012). Resolutions below 2–3 mm were obtained in all the different scenarios, supporting the feasibility of a prompt-photon-based beam range monitoring approach for PT using \(^{4}\)He, \(^{12}\)C or \(^{16}\)O particle beams.

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