Original paper

FLUKA simulation of target fragmentation in proton therapy

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ARTICLE INFO

Keywords:

Proton therapy

Target fragmentation

Monte Carlo simulation

ABSTRACT

In proton therapy, secondary fragments are created in nuclear interactions of the beam with the target nuclei. The secondary fragments have low kinetic energies and high atomic numbers as compared to primary protons. Fragments have a high LET and deposit all their energy close to the generation point. For their characteristics, secondary fragments can alter the dose distribution and lead to an increase of RBE for the same delivered physical dose. Moreover, the radiobiological impact of target fragmentation is significant mostly in the region before the Bragg peak, where generally healthy tissues are present, and immediately after Bragg peak. Considering the high biological impact of those particles, especially in the case of healthy tissues or organs at risk, the inclusion of target fragmentation processes in the dose calculation of a treatment planning system can be relevant to improve the treatment accuracy and for this reason it is one of the major tasks of the MoVe IT project.

In this study, Monte Carlo simulations were employed to fully characterize the mixed radiation field generated by target fragmentation in proton therapy. The dose averaged LET has been evaluated in case of a Spread Out Bragg Peak (SOBP). Starting from LET distribution, RBE has been evaluated with two different phenomenological models. In order to characterize the mixed radiation field, the production cross section has been evaluated by means of the FLUKA code. The future development of present work is to generate a MC database of fragments fluence to be included in TPS.

1. Introduction

In the interaction with the biological tissues, protons lose energy mainly by means of electromagnetic Coulomb interactions with electrons. The rate of energy loss per unit mass increases with depth as particles slow down reaching a maximum known as Bragg peak. In addition, nuclear interactions can take place with the atomic nuclei of the target material. At therapeutic energies of proton beam (60–250 MeV), only target fragmentation can occur.

Target fragments created in inelastic interactions of the proton beam with the target nuclei have low kinetic energy, high atomic number and high LET [1] as compared to primary protons [2]. So that, fragments alter the dose distribution, due to their short ranges that can spread in the order of 10–100 μm [3,4].

Target fragmentation increases RBE along the treatment irradiation

field with LET, as shown in several radiobiological measurements [5]. These characteristics make target fragmentation biologically relevant mostly in the region before the Bragg peak, where the cell inactivation due to ionization processes are less than nuclear interaction as compared to the Bragg peak region [3]. It results in RBE values significantly different from 1.1. i.e. the constant value currently used in proton therapy treatments, and does not consider target fragmentation. The topic of RBE variability in proton therapy is being widely debated in recent years, within this field, a widely supported hypothesis [3] is that secondary particles produced in target fragmentation could be one of the causes contributing to the increase of proton RBE [6].

The production cross sections of the target fragments are a topic of great interest but poor data are available: the direct measurement of target fragments is extremely difficult due to the short range of produced secondaries that have low probability to escape the target. The FOOT

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<https://doi.org/10.1016/j.ejmp.2020.09.018>

Received 30 October 2019; Received in revised form 2 September 2020; Accepted 20 September 2020

Available online 30 November 2020

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(FragmentatiOn Of Target) experiment [7–10] plans to use a complex experimental setup and an inverse kinematic approach to investigate the target fragments.

In the MoVe IT project [11], the effect of target fragmentation will be included in TRiP98 [12,13] TPS; the code is able to take into account the mixed radiation field for the description of biological effects of target fragmentation. In order to implement the transport of fragments in the TPS, a database for fragments fluence will be created.

In this paper, Monte Carlo (MC) simulations are performed to evaluate the amount of those target fragments with respect to primary protons fluence. The dose averaged LET has been evaluated in case of Spread Out Bragg Peak (SOBP) as well as the relative biological effectiveness by using the phenomenological models of Wedenberg [14] and McNamara [15]. The production cross sections of fragments at therapeutic energies have been evaluated by means of the FLUKA MC code. As the further step, FLUKA fluence spectra will be imported in TRiP98 TPS to evaluate the biological impact of fragmentation with a mixed field theory approach [13].

2. MoVe IT project

The aim of MoVe IT (Modeling and Verification for Ion beam Treatment planning) project is developing and testing innovative treatment planning models for particle therapy, accounting for a higher complexity of biophysical processes. The main effects that are going to be explored and implemented in MoVe-IT are: the biological impact of target nuclei fragmentation, RBE and intra-tumor heterogeneity.

In MoVe-IT project, the TPS modelling part is based on the use of TRiP98 (Treatment Planning for Particles) [12,13]: the first TPS for actively scanned heavy ions developed in the GSI pilot project on carbon ion therapy. Depth dose distribution, nuclear fragments spectra and stopping power data are the input of TPS. The biological effects of target

implemented in FLUKA. For the water phantom, we have defined the mean ionization potential as 77 eV using the MAT-PROP card to be consistent with TRiP98 value [19]. The FLUKA simulations were performed with 10^9 simulated particles, in 10 batches of 10^8 histories each.

4. Dose averaged LET and RBE evaluation

The dose averaged linear energy transfer (LET_D) is frequently used as a physical quantity to describe the biological effectiveness of mixed radiation fields [20]. LET_D is the dose-weighted mean value of the particle LET distribution at depth z in the radiation field consisting of dose contribution D_i from all particle species i :

$$LET_D(z) = \frac{\sum_i \int LET_i(E) D_i(E, z) dE}{\sum_i \int D_i(E, z) dE} = \frac{\sum_i \int LET_i^2(E) \phi_i(E, z) dE}{\sum_i \int LET_i(E) \phi_i(E, z) dE} \quad (1)$$

The quantities $LET_i(E)$ and $\phi_i(E, z)$ can be evaluated by FLUKA code and LET_D can be calculated using Eq. 1.

A Spread Out Bragg peak was simulated to homogeneously cover a $5 \times 5 \times 5$ cm³ target of water placed at $10 < z < 15$ cm. The initial proton energies were equally spaced in the range of $115.52 < E < 145.49$ MeV.

The evaluated dose distribution and the dose averaged LET as a function of depth are reported in Fig. 1. As expected, the dose averaged LET increases swiftly at the depth where the dose drops.

Literature offers several models to predict proton RBE based on dose averaged LET, dose and the tissue specific parameters α/β of the linear-quadratic model [21]. The most used phenomenological RBE models are Wedenberg [14], Wilkens [22], McNamara [15] and Carabe [23].

Starting from the dose averaged LET obtained with FLUKA simulation, the RBE has been calculated considering Wedenberg and McNamara models.

In the Wedenberg model, RBE is given by the formula [14]:

$$RBE(LET_D, D, (\alpha/\beta)_{ph}) = -\frac{1}{2D} \left(\frac{\alpha}{\beta} \right)_{ph} + \frac{1}{D} \sqrt{\frac{1}{4} \left(\frac{\alpha}{\beta} \right)_{ph}^2 + \left(qLET_D + \left(\frac{\alpha}{\beta} \right)_{ph} \right) D + D^2} \quad (2)$$

fragmentation can be evaluated as for projectile fragments using the available RBE model, in particular including LEMIV. Considering the contribution of each single fragment produced by a proton in water, the evaluation of total RBE is based on a mixed field approach [13].

3. FLUKA simulation

A Monte Carlo study has been performed with the FLUKA [16,17]

where q is a parameter obtained by experimental data, different for each cell line (for V79 cell line $q = 0.434$) and α/β represents the intrinsic radio-sensitivity of the irradiated cells [24].

Recently the RBE model of McNamara [15] has been derived considering the most comprehensive collection of proton RBE experimental data:

$$RBE(LET_D, D, (\alpha/\beta)_{ph}) = \frac{1}{2D} \left(\sqrt{\left(\frac{\alpha}{\beta} \right)_{ph}^2 + 4D \left(\frac{\alpha}{\beta} \right)_{ph} \left(p_0 + \frac{p_1}{(\alpha/\beta)_{ph}} LET_D \right)} + 4D^2 \left(p_2 + p_3 \sqrt{\left(\frac{\alpha}{\beta} \right)_{ph} LET_D} \right)^2 - \left(\frac{\alpha}{\beta} \right)_{ph} \right) \quad (3)$$

code which is often used as a reference in hadrontherapy [18] and has been benchmarked against measured data.

All simulations were performed with developer version using the PRECISION defaults card, physics card COALESCE to activate the coalescence mechanism and EVAPORATE card with evaporation of heavy fragments, which is recommended for the study of fragments production in proton therapy. The materials used are the default materials

where p_1, p_2, p_3 are experimental derived parameters assuming, for the pooled ensemble of cell lines, values of $p_0 = 0.99064, p_1 = 0.35605, p_2 = 1.1012$ and $p_3 = 0.0038703$.

In this work, the RBE has been calculated for the prescribed dose of interest of 2 Gy for a standard reference cell line, i.e. V79 (Chinese Hamster) $\alpha/\beta=2.7$ Gy [14].

In Fig. 2, the RBE has been evaluated with two different models and

Fig. 1. Energy deposited in target volume as function of depth (grey) and the dose averaged LET (red) in case of SOBP (the initial beams energy is in the range of $115.52 < E < 145.49$ MeV).

both have been calculated by considering the full radiation field (red lines) and only the primary protons (blue lines). In all analysed case, the RBE evaluated using Wedenberg is lower than McNamara in the region before the Bragg peak, while predicts higher RBE values in the distal region where both models significantly exceed the constant value.

The effect of the fragments considerations instead of only primary field is highlighted in the region before the Bragg peak and in the distal edge of SOBP (at depth $15 < z < 16$ cm), while becomes less evident in within SOBP where the predominant effect is the primary proton dose deposition. These results underline an underestimation of the biological dose in the entrance region and in the distal edge of SOBP, that as a potential consequence, in the healthy tissues may impact Normal Tissue Complication Probability (NTCP).

Therefore, an accurate knowledge of the target fragments production cross section is a fundamental requirement to correctly assess the biological dose of a proton beam. Waiting for FOOT experimental data [7], the different particle fluences of the mixed field has been studied for this purpose with FLUKA.

5. Production cross section

In order to estimate the contribution of target fragmentation, the production cross section due to inelastic interaction induced by proton beam in water has been evaluated using FLUKA code. The simulation is performed with proton pencil beams of different initial kinetic energies impinging on a thin water target. The target is a sphere of water with radius of $100 \mu\text{m}$. The considered initial kinetic energies are 50, 100, 150, 200 and 250 MeV in order to cover the range of therapeutic energies. The production cross section of each fragment produced by inelastic interaction in water has been scored. FLUKA is able to score the energy distribution by particle type with the USRYIELD card combined

Fig. 2. RBE as function of depth evaluated with Wedenberg (dashed line) and McNamara Models (solid line) considering the full radiation field (red) and the primary protons (blue). The grey line represent the constant $\text{RBE} = 1.1$ adopted in clinical treatments.

Fig. 3. Production cross section (CS) of inelastic interaction induced by a proton beam of 150 MeV (top) and 250 MeV (bottom) in water. The plots are in logarithmic scale.

with an AUXSCORE card. The AUXSCORE allow to select and distinguish the contribution of different particles.

In Fig. 3, the energy distribution of main fragments produced by proton beam of 150 and 250 MeV has been reported. In Table 1, the mean energies of each fragment are reported.

From these results, it emerges that fragments of ^4He , ^{10}B , ^{12}C and ^{16}O have low kinetic energies (few MeV) as reported in [3,4]. The production cross section evaluated with FLUKA will be validated with forthcoming experimental data acquired by FOOT and can be imported in the TPS for the transport of target fragments.

6. Fragments fluence

In order to include the impact of fragmentation and estimate the biological contribution of fragments in TPS, the secondary particles production has been evaluated with FLUKA code. In the simulation, the

Table 1

Mean energy (E_M) of main fragments produced by proton beam of 150 and 250 MeV (E_p) in water evaluated with FLUKA MC code.

Fragment	$E_p = 150$ MeV E_M (MeV/u)	$E_p = 250$ MeV E_M (MeV/u)
^1H	48.5	82.8
^2H	15.2	17.2
^3H	3.9	3.8
^4He	1.7	1.7
^{10}B	0.6	0.6
^{12}C	0.3	0.3
^{16}O	0.1	0.1

(a)

(b)

Fig. 4. Fluence of target fragments induced by 150 MeV protons in water at $z = 2.5$ (a) and 7.5 cm (b) (Bragg Peak at 15.8 cm).

source is a monoenergetic proton beam of 150 MeV. The water phantom is a cylinder of radius 20 cm. The scored quantity is the fluence of each fragments at different depths in a water phantom. FLUKA scores the track-length fluence distribution of certain particle with the USRTRACK card combined with an AUXSCORE card. The fluence has been evaluated at different depths in a volume (radius $r = 20$ cm, height $z = 0.1$ cm and volume $V = 125.6$ cm³): the radius of target was chosen in a way that the full energy of the beam would be deposited inside the volume.

In Figs. 4 and 5, the fluence of fragments produced by a proton beam of 150 MeV in water has been reported at different depths. The fluence of all protons is characterized by two components: the primary particles (the region with peak) and the secondaries protons (the plateau region). Due to the energy dependence of the nuclear interaction, the energies of fragments are higher in the entrance channel than the Bragg peak region and decrease with increasing depth. In Bragg region, the effect of fragmentation is less important than ionization processes and the produced fragments have such a low energy to become inefficient biologically [3]. Therefore, target fragmentation is more relevant in the region before the Bragg peak.

From the results shown in Figs. 4 and 5, it emerges that the main contributors to the target fragmentation are Hydrogen isotopes, according to [25,26], but a significant contribution to the dose distribution is given also by Helium fragments, as shown in [27].

7. Conclusions

The full particle spectrum of proton beams at therapeutic energies in water has been presented and characterized in this work based on a

(a)

(b)

Fig. 5. Fluence of target fragments induced by 150 MeV protons in water at 12.5 (a) and 15 cm (b) (Bragg Peak at 15.8 cm).

FLUKA MC study. For most abundant target fragments, fluence has been studied as well as cross sections and mean production energy, to allow evaluation of the relevance of these secondary particles in a biological dose calculation. Simulations results evidence that secondary protons are the most abundant target fragments; their production rate is two orders of magnitudes higher than ⁴He, the second most relevant species.

A first estimation of the biological impact is given by evaluating the dose averaged LET for a SOBP in therapeutic energy range, with Wedenberg [14] and McNamara [15] RBE models. RBE results to be greater than 1.1 in the entrance channel, before reaching the well known maximum in the distal edge of SOBP, underlining an underestimation of the biological dose in the healthy tissue region.

For a more dedicated analysis of the biological impact a full mixed field approach is necessary, beyond the pure LET_D based approximation, which has been reported to be often insufficient [28]. In the framework of the MoVe IT project, on the basis of these simulations, the creation of a detailed fragments database is now possible for the inclusion of target fragmentation effect in a biological TPS. Using TRiP98, the biological effects of target fragmentation can be evaluated with LEMIV model. A systematic analysis of the biological impact of such fragments, with a mixed field approach, will be subject of a forthcoming paper.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This work was supported by Istituto Nazionale di Fisica Nucleare (project MoVe-IT).

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