Volume 20, No 3 | International Journal of Radiation Research, July 2022

Monte Carlo simulation of a new proton therapy technique using bio-nanoparticles and high energy proton beams

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► ***Original article***

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Received: June 2021
Final revised: December 2021
Accepted: January 2022

Int. J. Radiat. Res., July 2022; 20(3): 615-619

DOI: 10.52547/ijrr.20.3.14

Keywords: *Monte Carlo simulation, proton therapy, bio-nanoparticles, rotary accelerator.*

ABSTRACT

***Background*:** Currently, many researchers focus their work on the effects of bio-nanoparticles inside the tumor during proton therapy. Indeed, these bio-nanoparticles enhance the absorbed dose especially if they have been settled at the Bragg peak zone. The main goal of this study is to give a new technique that improves and facilitates the clinical protocol during proton therapy for brain tumors by adding nanoparticles to the tumor and using a rotary accelerator with high energy (200 MeV). ***Materials and Methods*:** With the use of the Monte Carlo Geant4 code, we simulated a proton therapy of a tumor located in the center of a human head containing bio-nanoparticles. The proton beam energy was chosen large enough to avoid having Bragg's peak at head level. ***Results*:** The results revealed that there was an optimization in the deposited energy at the tumor, at the same time the deposited energy at healthy tissue was less compared to ordinary proton therapy. It also showed that the platinum is the most effective bio-nanoparticles used in this work. ***Conclusion*:** The addition of bio-nanoparticles to tumors and the use of a high-energy (200 MeV) rotary accelerator improve and facilitate proton therapy. This new technique allows the direction angle of the proton beam to be changed regardless of the position of the tumor, making it effective against moving tumors and preserving healthy tissue. In addition, the dose deposited in the tumor can be increased just by pivoting the head of the accelerator around the organ.

INTRODUCTION

Nowadays, most scientific research is focused on tumor therapy because of the high number of cancer deaths. The number one cause of death before the age of 70 is cancer according to the World Health Organization [1]. Surgery has been the best cancer therapy, but this treatment is very risky in the case of tumors inside deep and sensitive organs. External ionizing radiation is another form of therapy where both the tumor and the healthy tissue receive a high dose of X-ray radiation. On the contrary, proton therapy is the most suitable choice for such complex and deep tumors. Indeed, the proton beam deposits the majority of its energy in a very narrow zone called Bragg Peak (BP), about a few millimeters. In the clinical field, proton therapy is used the most for deep tumors and Pediatric treatments [2]. The use of cyclotrons and synchrotrons to accelerate charged particles in hospitals for cancer treatment is increasing, the developments of the charged particle accelerator, in particular the proton and carbon ion beams, have allowed its use in the treatment of tumors [3]. Nanomedicine is generally considered a promising area of research with interesting perspectives in the subjects of diagnosis and the clinical treatment of patient diseases. The bio-distribution behavior and toxicological effects of new nanoparticles (NPs) need to be carefully evaluated before their actual clinical use [4]. Indeed, nanomedicine hopes to improve and bring together new nanomaterials for various biomedical applications such as: drug delivery vehicles, imaging agents, biosensors and therapeutic agents. The presence of gold nanoparticles (AuNP) in the tumor boosts the cross section of the stopping power of incident energetic protons and the photoelectric effect for X-ray absorption, allowing to deposit a higher dose [5, 6]. AuNPs, as high Z particles, have the capability to increase the dose accumulated in targeted tumors by absorbing more ionizing radiation. In addition, AuNPs convert non-ionizing radiation into heat, because of the Plasmon resonance, achieving about hyperthermic annihilation to cancer cells [7]. Jong-Ki Kim *et al.* carried out an experimental study on enhancement proton therapy in mouse tumors by the effects of metallic nanoparticles. They noticed that the proton alone slowed tumor growth, whereas those who received 100 to 300 mg/kg injections of AuNP or Iron

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nanoparticles (FeNP) are more likely to survive longer [8]. The use of gold nanoparticles during proton therapy has characteristics of charged particle interactions that are modified and causes further radiological destruction to the growth or tumor [9]. Several studies conducted inside and outside the laboratory have reported irradiation with AuNPs has further damaged the tumor cells [10, 11]. During a proton therapy, about 30% or more of the energy proton beam is deposited on a narrow zone where the tumor is found, named the Bragg peak [12]. Furthermore, the position of the BP relies heavily on the proton beam energy. Therefore, the primary energy of the proton beam ought to be taken carefully by the medical staff in order to sweep the entire tumor by the corresponding BP. In clinical medicine [13], pencil beam and passive scattering were the two strategies of proton therapy used until now. In the primary strategy, the proton beam is refracted with a variable magnetic field to produce a monoenergetic pencil beam and scan it across the tumor [14]. The subsequent procedure depends on a single energy proton beam scattered by foil (made of lead or other material to broaden the beam). Both technique options take additional time for the medical staff and should be used carefully for every patient. There are many Monte Carlo codes available such as; the Geant4 toolkit [15, 16], PENELOPE [17] and other codes to be used in Radiation medical simulation. When using these codes, we can compute Linear Energy Transfer (LET) [18] and study the biological effects of radiation like the Relative Biological Effectiveness (RBE) which is the ratio of the absorbed dose of a reference radiation [19]. The purpose of this work is to present a Monte Carlo simulation of a novel technique that we suggest in order to facilitate the control of proton therapy. Our idea is not like previous studies which were interested in Bragg peak. In this work we injected nanoparticles inside the tumor in order to further increase its density and used a rotary accelerator with a high energy proton beam to avoid the BP and the risk of touching healthy organs. All details have been described in the following paragraphs.

MATERIALS AND METHODS

This study was effectuated at the Radiation Analysis and Application Laboratory (LAAR) in our university. Our fundamental goal of this work is to investigate the impact of bio-nanoparticles (BNPs) inserted into a tumor during high Proton Beam Energy (PBE). For this research, we used Geant4 code to simulate a sphere-shaped tumor 1.5 cm in diameter, located in the center of an adult phantom head, in which we added small amounts of concentrations of nanoparticles in the tumor, between 20 ppm and 200 ppm. These quantities of nanoparticles have been taken in such a way as to avoid any kind of toxicity caused by these BNPs. The BNPs used in this simulation are gold nanoparticles (AuNPs) and platinum nanoparticles (PtNPs). Several researchers use these NPs during proton therapy because of their biocompatibility. Until now, no experience has been done on humans concerning the use of nanoparticles during proton therapy or radiotherapy, only on animals. Placed at 1 meter from the patient, the phantom head is exposed to a monoenergetic proton beam (see figure 1). As this figure shows, we have placed the source of the proton beam 1 meter from the phantom head, in which we can rotate the accelerator head around our phantom head. In this simulation, we took four positions.

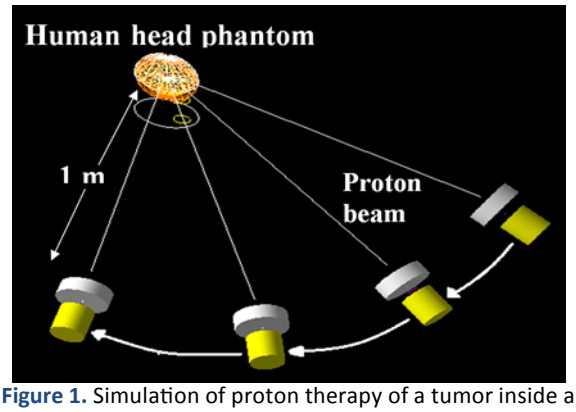


Figure 1. Simulation of proton therapy of a tumor inside a head using a rotary accelerator with a monoenergetic proton beam of 200 MeV.

The Geant4 Monte Carlo toolkit

The Geant4 code (version 10.6) was the method used on our simulation. This code is a platform using Monte Carlo methods to mimic the path of particles through matter. Geant4 is open-source simulation toolkit approved by numerous collaborators in various disciplines. The areas of application of Geant4 include high energy physics, medical physics, space science, and astrophysics. This work is based on the G4HadronHElastic and G4HadronInelasticQBBC Physics model [20]; these packages contain electromagnetic and hadronic processes. The human head geometry is composed essentially of a skeleton with a thickness of 8 mm and brain. Soft tissue, with a thickness of 2 mm, then covers the skeleton. At the center of the brain is where the tumor is placed. The Geant4 database is where the chemical compositions and densities of soft tissue, skeleton, brain, and tumor are taken from. Then RBE in the case of 125 MeV was calculated by equation 1:

$$RBE(125MeV) = \frac{EDP\ with\ NPs\ (PBE\ of\ 125\ MeV)}{EDP\ without\ NPs(PBE\ of\ 125\ MeV)} \quad (1)$$

And the RBE in the case of 200 MeV was calculated by equation 2:

$$RBE(200MeV) = \frac{EDP\ with\ NPs\ (PBE\ of\ 200\ MeV)}{EDP\ without\ NPs(PBE\ of\ 125\ MeV)} \quad (2)$$

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Where
RBE is the Relative Biological Effectiveness;
EDP is the Energy Deposited;
NPs is the Nanoparticles;
PBE is the Proton Beam Energy.

Statistical analysis

For a better analysis and accurate visual comparison of results, we used ROOT (Data Analysis Framework) to create the corresponding charts, then from this results we calculated the RBE.

RESULTS

The spectrum of primary proton particles

Proton therapy is one of the most accurate external radiation therapies, due to the Bragg peak. About more than 40% of the proton beam energy is deposited in a small area. For the case of a tumor that is located inside a human head, the appropriate proton beam energy which corresponds to the Bragg peak in the tumor area should be taken 125 MeV. In the clinical field, looking for the energy of the proton to detect the Bragg peak in the tumor area requires hard medical protocol. Usually, it takes more time and is uncomfortable for patients. Moreover, one of the main problems is the change in tumor size or displacement during the diagnostic days. We performed a Monte Carlo proton therapy simulation for an intracranial tumor, in which nanoparticles were injected. These nanoparticles will increase the density of the tumor and thus improve energy absorption. Figure 2 shows the plot of the deposited energy in a tumor located in the center of a human head both with and without nanoparticles. From this figure, for a PBE of 200 MeV the allocation of the energy deposited at the level of the tumor is homogeneous. Moreover, it does not depend on the position of the tumor.

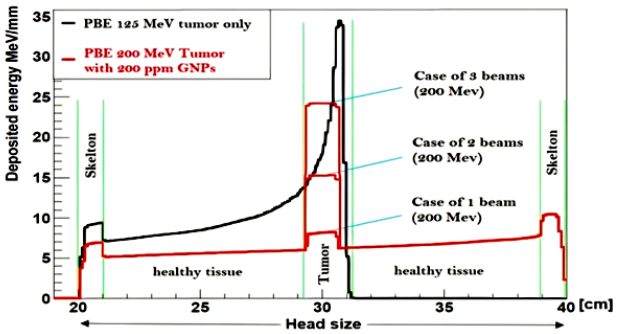


Figure 2. The energy deposited along the head.

These results show that this new technique considerably facilitates proton therapy. To increase the energy deposited in the tumor, a rotary accelerator can be used or the patient must be pivoted carefully during the proton therapy. This technique facilitates the medical protocol and presents no risk of depositing great energy in healthy areas compared to Bragg peak energy. In addition, the deposited energy in healthy areas with high proton energy of 200 MeV is less than ordinary proton therapy with energy of 125 MeV. This can be in favor compared to ordinary proton therapy.

Then we calculated the RBE for the case of ordinary proton therapy (the BP at level of the tumor), where the PBE is 125 MeV and in this case we found that the RBE is equal to 1,01196 when we added 20 ppm of AuNPs and equal to 1,01120 when we added 20 ppm of PtNPs. For our case, where the PBE is 200 MeV and we kept the same concentration of NPs, we found that the RBE is equal to 0,29156 when we used AuNPs and equal to 0,29172 when we used PtNPs. However, when we rotated the head of the accelerator and exposed the tumor from 4 different positions, the RBE increased to 1,16624 with AuNPs and to 1,16688 with PtNPs.

The spectrum of secondary particles

During proton therapy, the interaction of the proton beam with an organ such as a human head leads to secondary particles, mainly neutrons and X-rays [21]. These secondary particles result from the loss of energy from the primary proton beam during their paths. In fact, during our simulation, Binary and Bertini cascade processes have been taken into consideration (both elastic and inelastic models) to produce secondary neutrons, photons and all charged particles processes.

Secondary X-rays from primary proton

Secondary charged particles such as electrons or positrons formed along the path of the primary protons produce X-rays. These particles are produced from inelastic collisions of primary protons with atoms in human organic tissue. Figure 3 shows no difference of secondary X-rays at the output of the head for the concentrations taken in our simulation.

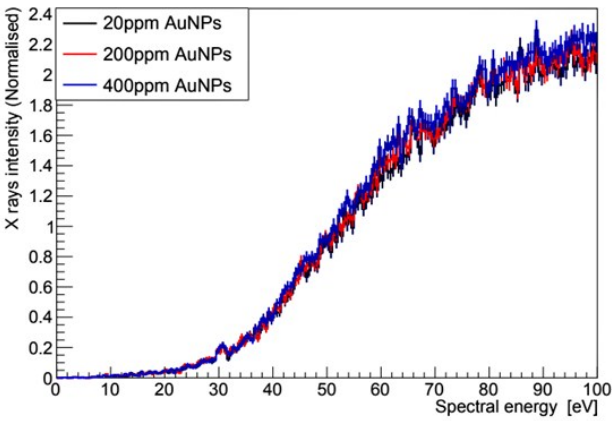


Figure 3. Spectrum of secondary X-rays from proton beam energy of 200 MeV for 20 ppm (respectively 200 ppm and 400 ppm) concentrations.

Auger-electrons spectrum

To better understand the effect of nanoparticles on the increase of the dose, we have been interested

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in the effect that nanoparticles have on the tumor. For this, the kinetic energy of the proton beam arriving close to the tumor was observed equal to 98 MeV. Figure 4 shows the Auger-electrons spectrum obtained from a proton beam of 200 MeV energy. As it can be seen, the intensity of Auger-electrons spectrum in the case of 200 ppm AuNPs concentration is almost 10 times greater than for 20 ppm AuNPs concentration.

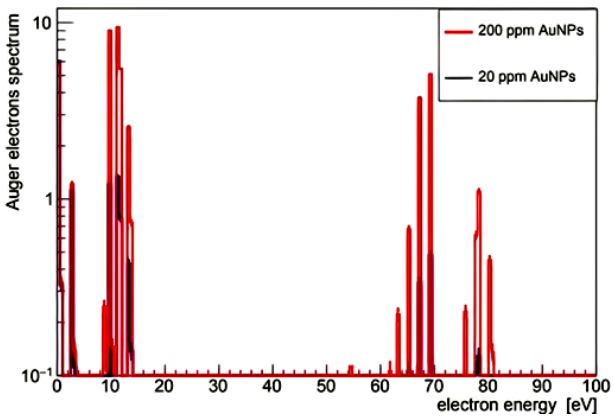


Figure 4. Auger-electrons spectrum resulting from proton beam energy of 200 MeV for 20 ppm and 200 ppm of AuNPs concentrations.

DISCUSSION

Proton therapy is used in two ways: passive diffusion and pencil beam. Both of them should be used carefully. Our main goal is to optimize the energy deposited in the tumor and facilitate the clinical practice of proton therapy. Proton therapy of a tumor located in the center of an adult human head requires energy around 125 MeV to ensure that the Bragg peak coincides with the tumor. In clinical practice, the choice of proton beam energy is highly dependent on the location of the target tumor. Therefore, rotating the accelerator head makes the task more complicated. We have realized a simulation of a new proton therapy technique. This technique is based on the principle of adding high Z nanoparticles to the tumor and using a high-energy proton beam in such a way that the Bragg peak doesn't occur. For this, the proton beam energy has been equal to 200 MeV which is high, safe, and feasible; this was proven by the study carried out by Takashi Ono et al. [22]. From Figure 2, it is well noted here that this new technique is sweeping the tumor well and at the same time minimizes the deposited energy in healthy tissue. Furthermore, to increase the deposited energy at the tumor level without affecting healthy tissue, we can simply rotate the accelerator carefully at several angles while keeping the same energy of the proton beam and rise the concentration of NPs, because the result in the figure 4 explains how AuNPs enhance the dose during proton therapy and this result is on good agreement with result of Cho *et al*. whom noticed that Auger electrons increase the dose and only at short distances [23]. Moreover, from the figure 3, we have not noticed any X-ray emission (PIXE) due to the existence of AuNPs into the tumor. This can be explained by the addition of a small number of nanoparticles into the tumor. Indeed, the RBE has been calculated in both cases, with our new technique and ordinary proton therapy technique based on Bragg's peak energy. We have noticed here that the RBE has been increased by about 16% compared to the ordinary technique. As the results showed, a low concentration of NPs improves the RBE. The peculiarity of our technique is that we have the possibility of increasing the RBE by rotating the accelerator source around the phantom head while using low concentrations of NPs. We mention that in the case of the new technique the accelerator's head is considered as rotary and we have taken only four positions. To avoid toxicity, our simulation is based on 20 ppm NPs. With this quantity, the PtNPs are still the best NPs should be used in the proton therapy as also found in other studies [24, 25].

CONCLUSION

We can conclude from these results that the addition of bio-nanoparticles to tumors and the use of a high-energy (200 MeV) rotary accelerator improve and facilitate proton therapy. This new technique allows to change the direction angle of the proton beam regardless of tumor position and sweep it all, making it effective against moving tumors and preserving healthy tissues. However, all aspects discussed above need to be further explored before using the treatment with protons on humans to achieve victory in the fight against cancer.

ACKNOWLEDGEMENTS

This work was supported by the DGRSDT (General Direction of Scientific Research and Technological Development), Ministry of Higher Education and Scientific research, Algeria.

The authors would like to thank Professor M. Ketel from the University of Baltimore, Maryland, USA and Dr A. Attili from the National Institute of Nuclear Physics (INFN) Italy, for the fruitful discussions and the help they provided the authors.

Funding: This work was supported by the DGRSDT (General Direction of Scientific Research and Technological Development), Ministry of Higher Education and Scientific research, Algeria.

Ethics approval and consent to participate: This study was approved by the medical ethics committee of and was based on the Helsinki Declaration.

Author contributions: Data All authors contributed equally to this study, data curation and analysis and the writing of the manuscript. All authors read and

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approved the final manuscript.
***Conflicts of interest*:** Declared none.

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