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Role of GNPS on the Enhancement of Proton Therapy of Breast Tumor Using MCNPX Simulation

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ABSTRACT

Background: The beam therapy plays an important role in the treatment of cancer, which is the most common and successful form of treatment used after surgery. In proton therapy, proton beam (PB) particles irradiate the tumor. To enhance the treatment of breast tumor it is possible to inject gold nanoparticles (GNPS) into the tumor at the same time as irradiating the PB. The aim of this paper is the simulation of the treatment of breast tumors by using PBs and injecting GNPS with different concentrations, simultaneously. Therefore, we introduce the breast phantom (BP), then we irradiate it with a proton pencil beam, which is also injected with GNPS at the same time. In order to show the enhancement of the absorbed dose in the tumor, we use MCNPX.2.6 code. **Results:** The findings of our simulations show that the location of the Bragg's peak within the tumor shifts to higher depths with increasing energy. Also, by injecting GNPS in different amounts of 10, 25, 50 and 75 mg / ml with simultaneously irradiation of the PB, the rate of absorbed dose increases up to 1.75% compared to the non-injected state. Our results also show that the optimal range of proton energy that creates Bragg peaks within the tumor is between 52 to 65 MeV, which causes the creation of spread out of Bragg peak. It should be noted that the amount of absorbed dose is affected by quantities such as total stopping power, average Coulomb scattering angle, CSDA range and straggling range. **Conclusion:** This work offers new insights based on the use of GNPS in the treatment of breast cancer through proton therapy and indicates that the addition of GNPS is a promising strategy to increase the killing of cancer cells while irradiating fast PBs. In fact, the results of this study confirm the ability of GNPS to enhance treatment by increasing the absorbed dose in breast tumors using proton therapy.

Key words: tumor, proton therapy, GNPs, breast, enhancement

INTRODUCTION

Nowadays, hadron therapy with heavy charged particles is a modern technique in radiotherapy, so that it has physical and radiobiological advantages and in general has useful clinical properties. Physically, due to the optimal dose distribution of heavy charged particles, healthy tissues can be significantly protected from unwanted damage, which in turn reduces side effects and secondary cancers. In addition, from a radiobiological point of view, the RBE of these particles is higher than that of photons, thereby increasing the efficiency of killing cancer cells and increasing the probability of tumor control. Thus, this technique is considered as the preferred and definitive method in terms of cancer treatment. From a DNA damage perspective, it can be argued that cancer treatment uses the proton hadron beam to damage the DNA of cancer cells without destroying healthy cells. However, in X-ray therapy, nearby non-cancerous cells are also destroyed.

In recent years, using of high-z NPs for tumor activation in order to increase absorbed dose inside it are presented and different studies are performed on the effects of NPs such as gold, silver, platinum, and gadolinium that are combined with ionizing radiation. [1-3] If GNPs

with high Z target tumor, they can increase specifically absorbed dose with a focus on tumor, and thereby minimizing the radiation damages on the healthy tissues. [4] Lin, et.al used Monte Carlo simulations to differentiate between two types of interactions: nanoparticle interactions on the photons and protons respectively; they found that the former increased more significantly than the latter. [5] Lin, et.al presented a biological model in which protons require the NPs with higher concentrations compared with photons to have the same effectiveness. [6] Butterworth et al., Porcello et al., [7] and Jane et al. [8]. Investigated on the simulations of Gold (Au), Silver (Ag) and Platinum (Pt), and confirmed that these materials are compatible with each other to participate in treatment. [9] Gao and Zheng studied on Monte Carlo simulation, in which they simulated a water phantom on a GNP. They concluded that the production of secondary electrons is increased with reducing of proton energy. Kewon et al. simulated a GNP in water. [10] In addition, they proposed a radial dose distribution with respect to secondary electrons. They noticed that the effect of GNPs increased more than a few micrometers in length and a few nanometers in radius direction, respectively [11].

In this study, we used MCNPX.2.6 simulator while employing the technique of pencil beam to radiate proton toward the PB for the first time. As a matter of fact, the absorbed dose and other quantities were examined in two cases: when GNPs were not injected into the PB, and when GNPs were injected into it with selecting four concentrations of 10, 25, 50 and 75 *mg/ml*. Since that the Coulomb scattering effect is one of the important physical phenomena, we determine the mean scattering angle in both cases, and compare the results.

In this work, we use the MCNPX.2.6 code simulator for the first time with the proton irradiation method to the suggested PB, so that we can determine the absorbed dose and the related various quantities (mass stopping power, proton beam energy deposited, flux of generated secondary particles, absorbed dose, spread out of Bragg's peak, MCS, CSDA range and straggling proton range) in this phantom in the following two steps. In the first step, GNPs are not injected into the tumor, while in the second step, GNPs with 4 different concentrations of 10, 25, 50 and 75 *mg / ml* are injected into the tumor.

Results and discussion

In Figs.1 to 9 we represented the results of the total mass stopping power, proton energy deposited ,flux of secondary particles, absorbed dose, spread out of Bragg's peak, mean Coulomb scattering angle, CSDA range variations and range straggling in terms of proton energy at the range of $3 \leq E(\text{MeV}) \leq 250$ in breast tissue through MCNPX.2.6 simulation for two cases: a:with and b:without injecting of GNPs, respectively.

Figure1: Comparison of total mass stopping for with / without injecting of GNPs for different concentrations at BP

As shown in Fig.1, by increasing the proton energy the stopping power is reduced and with increasing the concentration of GNPs its value is enhanced. This is due to the density effect and also the production of secondary electrons, which means that collisions with respect to distance between the charged particles and the atomic electrons are influenced by their atoms interference. These atoms are polarized in the electric field of the charged particles so that reduce the electron's electric field in the distance of collision, thereby reducing the stopping power. Since the relativistic effects highlight the collisions with distance, this effect can be clearly seen at the high energy levels. This effect depends on the number of polarized atoms per volume and, consequently, on the density of the materials, and therefore they are called as the density effect. Typically, the ratio of the mass stopping power changes slowly in two materials with the particle energy. Also, if one of the given material is solid and the other one is liquid or gas, this ratio will change due to the reduction in the mass stopping power of solid when the particle energy approaches the relativistic limits.

According to the numbers in Table 1 and the our selected phantom, the energy variations of the proton beam in terms of spatial changes x and y in breast tissue containing a spherical tumor with 1 cm diameter for both without and with injecting GNPS into the tumor are given in Fig2a and b. According to these figures, it can be seen that a proton beam in the direction of the tumor is irradiated from the outside to the tumor and the its maximum energy deposited at the end of the tumor, in which it is seen in dark red color. As can be seen from these figures, the adjacent tissues around the tumor inside the breast are also irradiated to less proton radiation, the color range of which is yellow to orange. The tissues farther behind the tumor (part of the breast tissue, chest, right lung, etc.) receive less energy deposited, their color range is from blue to green, as well as areas that are farther away from the tumor and energy is not deposited in them .is seen in white. From comparing these figures, we see that with injecting GNPS to tumor with amount of 75mg/ml the deposited energy is increased.

b

Figure 2: proton beam energy deposited a)without b) with injection of GNPS, (75ml / mg) in terms of spatial changes x and y in the right breast tissue containing the tumor

When protons are absorbed by a nucleus in an interaction, other particles are released as products by the nucleus. These released particles are called secondary particles such that are: protons, deuterons, lighter nuclei such as alpha and the recoil nuclei, gamma photons and neutrons. Each of these generated particles transport some of the initial energy. Deuterons and heavier ions carry much smaller amounts of dose. In total, they make up about 1% or less of the therapeutic absorbed dose, and their energy and range are very small, and they discharge their kinetic energy in a localized manner and very close to their point of origin. Therefore, the dose of secondary particles such as neutrons, electrons, alpha and protons was evaluated here for without and with injecting GNPS.(see Figs3 and 4)

Figure 3: Flux of generated secondary particles of electron , alpha , proton and neutron in terms of energy of the produced particles without GNPS injection

Figure 4 : Flux of generated secondary particles of electron , alpha , proton and neutron in terms of energy of the produced particles with GNPS injection(75mg/ml)

From these figures we see that with jncreasing GNPS up to 75mg/ml the flux of secondary particles produced such as electron , alpha , proton and neutron are increased respect to without of GNPS injection.

In Figures 5a and b, the diagrams of absorbed dose variations in tumor-containing breast tissue in terms of the penetration depth of proton beams for different irradiated beam energies in the range of 52 to 65 MeV for the two states without / with injection of GNPs are given. As can be seen from these figures, in the energy range of the proton beam, the absorbed dose into the tumor occurs, and with increasing the energy of the proton beam, the absorbed dose into the tumor decreases with increasing penetration depth into the tumor. Injection of GNPs in the amount of 75 mg / ml increases the absorbed dose compared to the non-injection mode.

a

b

Figure 5: absorbed dose variations into breast tissue containing tumor in terms of penetration depth of proton beams for different energies of radiant beams (each beam contains 10^6 protons) a) without b) with injection of GNPS.

In order to find the proper range of energy to completely cover the tumor volume, the beam energy was increased step by step. Since the Bragg's peaks are narrow on their own and are not suitable for covering any target, the spread out of Bragg's peaks was formed. For this purpose, the number of peaks required to participate in the construction of the spread out of Bragg's peak was calculated until a uniform and maximum dose is delivered to the tumor. Therefore, in Figures 6a and b, we show the diagram of the variations of the spread out of Bragg's peak in terms of penetration depth of the proton beam inside the breast tissue containing the tumor for without and with the injection of GNPS. Such that at a depth of penetration of 3 to 4 cm, i.e within a spherical tumor with a diameter of 1 cm, the spread out of the Bragg's peak occurs.

b

Figure 6: Variations of spread out of Bragg's peak in terms of penetration depth of the proton beam into the breast tissue containing tumor a) without b) with injecting of GNPs.

By comparing Figures 6a and b, it can be seen that the range of spread out of Bragg's peak increases with the injection of GNPs.

Figure 7: Comparison of the mean Coulomb scattering angle in terms of proton energy in the range of $3 \leq E \text{ (MeV)} \leq 250$ for the injection of different concentrations of GNPs in the PB

As it can be seen in Fig.7, if the radiation proton energy increases, the magnitude of θ_0 will be increased in all states; however, the minimum θ_0 in the breast tumor is related to non-injection GNPs whereas this amount is gradually increased when the injected concentration of NPs is increased into breast tumor.

Figure 8: CSDA range variations for with / without nanoparticle injection as a function of incident proton energy

As it is shown in Fig.8, without injection of GNPs has the highest CSDA range, and it is slightly decreased when GNPs are increasingly injected so that CSDA range will be approached to its minimum amount at concentration of 75 mg/ml.

Figure9: The comparison between variations of range straggling versus proton energy in the range of $3 \leq E$ (MeV) ≤ 250 (with/without GNPs in the breast tissue)

As it is shown in Fig. 9, range straggling is increased with the enhancement of proton energy for with / without GNPs. But the maximum value of this quantity is devoted to without GNPs injection and the minimum amount of range straggling is related to 75 mg/ml GNPs injection. It means that with increasing the amount of GNPs injection, the straggling range is reduced.

Conclusion

In this work, the MCNPX.2.6 simulation code was used in the treatment of a given tumor inside the BP. Due to the depth of the tumor, the appropriate range of proton energy to cover it was 52 MeV to 65 MeV. The proton absorbed dose in other

tissues of the body was lower than the absorbed dose received by the tumor. The flux of secondary particles in healthy organs is much smaller than the flux of protons received by the tumor, but it is better not to ignore it because the secondary particles release a lot of their energy before reaching the tumor, which can be a risk factor. All of these cases confirm the benefits of proton therapy for primary and non-surgical cancers, but the side effects of generated secondary particles, especially neutrons, are higher than those of other secondary particles and have a higher relative biological effect than electrons and alpha, and by creating more ionization can have a more destructive effect on cells. Therefore, further studies are needed. Also, the results of our simulations show that the injection of GNPS up to a maximum of 75 mg / ml increases the absorbed dose in tumor and increases the secondary particles produced, which enhances the treatment of breast cancer.

Methods

Since the purpose of this paper is the simulation of particle therapy of breast cancer tissue using PB radiation with injecting of GNPs, the following items are studied to achieve this goal.

Suggested right BP containing tumor

The Monte Carlo simulations were done using MCNPX (Monte Carlo N-particles extension) version 2.6, which can handle the interaction and transport of protons, neutrons, electrons, and other particles over a vast range of energies. In the current study, to investigate the analytical phantom of the human body, based on ORNL publications, ORNL-female phantom was used to create the input file for the MCNPX transport code. Figure 10 illustrates the scheme

of this phantom. The original ORNL phantom, the breast tissue was considered as soft tissue, and for all soft tissues, a unique material had been used. However, it is well known that the material composition of breast tissue is different from other soft tissues. Hence, the breast material was improved. The breast material composition used in the current study for ORNL phantom is presented in Table 1. The spherical tumor is located at a radius of 0.5 cm and at a depth of 3 cm from the breast. (Figure 10). Note that according to the coordinates shown in Figure 10, the coordinates of the center of the selected tumor are $x = -10$ cm and $z = 52$ cm and $y = -10$ cm which we have simulated using this code. By properly squeezing the breast, the tissue is evenly expanded, its thickness is reduced, and the irradiated time is reduced. The defined source is a single energy point source that is irradiated at a distance of 0.5 cm from the phantom perpendicular to the breast and in the direction of the tumor from 52 to 65 MeV energy with a step of 1 MeV and finally to calculate the absorbed dose in terms of penetration depth in the tumor range was used from Cartesian mesh with a thickness of 1 mm.

Then, we would transport the PB at the range of $3 \leq E \text{ (MeV)} \leq 250$ toward the phantom, and would examine the effect of this beam on the breast tumor. The source defined in this work is a circle with a radius of 25.0 mm, which has a Gaussian energy distribution, and it is close to the phantom. In this work, we insert the NPs into the tumor tissue using a mechanical injection method. Simultaneously, by injecting GNPs into cancerous tissue, a PB irradiates

the phantom. Then we estimate the absorbed dose related to the two states i) without and ii) with injecting GNPs with PB radiation. Finally, we confirm the effect of increasing the absorbed dose in the tumor by injection of NPs.

a

b

Figure 10: a) Frontal view of the right breast phantom b) display of Cartesian coordinates of the selected right breast phantom containing a spherical tumor of 1 cm diameter with adjacent tissues.

Table 1: Percentage of human tissue constituents in all phantoms except infant

lung	skeleton	Soft tissue	element
10.134	7.337	10.454	H

10.238	25.475	22.663	C
2.866	3.057	2.49	N
75.752	47.893	63.525	O
0	0.025	0	F
0.184	0.326	0.112	Na
0.007	0.112	0.013	Mg
0.006	0.002	0.03	Si
0.08	5.095	0.134	P
0.225	0.173	0.204	S
0.266	0.143	0.133	Cl
0.194	0.153	0.208	K
0.009	10.19	0.024	Ca
0.037	0.008	0.005	Fe
0.001	0.005	0.003	Zn
0.001	0.002	0.001	Rb
0	0.003	0	Sr
0	0	0.001	Zr
0	0.001	0	Pb
0.296	1.4	1.04	Density(g/cm³)

Stopping power and absorbed dose

The energy loss of ions in a material is the main factor for determining of ions distribution. Since ion loses its energy (E) at the penetration depth (x), where x is the distance inside the target, which is measured from the target level, the lost energy in a material is called stopping power, which is represented by dE/dx. An energetic ion penetrating into a material essentially loses its energy via two ways: a) nuclear energy loss (dE/dX_{nuc}) (b) electronic energy loss (dE/dX_{el}); they are independently examined. Thus, total power(S) is given by:

$$S = dE/dx = \frac{dE}{dx_{nuc}} + \frac{dE}{dx_{el}} \quad (1)$$

The equation for the proton stopping power in a material is obtained by the quantum mechanical Bethe's equation [12]:

$$\frac{dE}{dx} = \frac{nz^2e^4}{4\pi\epsilon_0^2m_e v^2} \left[\left\{ \ln \left(\frac{2m_e v^2}{I} \right) \right\} - \ln \left(1 - v^2/c^2 \right) - v^2/c^2 \right] \quad (2)$$

Where, Z= heavy ion atomic number, e=elementary charge, n= number of electrons per unit volume of matter, c= the speed of light in vacuum, $\beta = v/c$, where v is the ion velocity and c is the light velocity in vacuum, I= the mean excitation potential, ϵ_0 = vacuum permittivity, and m_e = electron mass. Mass stopping power is obtained by: $\frac{1}{\rho} S = -\frac{1}{\rho} \frac{dE}{dx}$. In Fig.2, we compare the total mass stopping power of proton in PB using MCNPX.2.6 simulation for two cases: a) without b) with injecting of different concentrations of GNPs. The absorbed dose is defined

as the mean energy deposited in matter by ionizing radiation per unit mass. The absorbed dose is in Gray (Gy) in radiotherapy. It is given by:

$$D = 1.602 \times 10^{-10} \cdot F \cdot \frac{S}{\rho} \quad (3)$$

Where ρ is the density of the absorber material while F is the number of charged particles (proton) per unit cm^2 . The Fig.3 compares the absorbed dose of two cases a) with and b) without injecting of GNPs as a function of the penetration depth at different proton energies in the PB. It should be noted that at this simulation work: $F = 1 \times 10^6 \frac{\text{number of particles}}{cm^2}$.

Multiple Coulomb scattering

Protons that are able to pass through material may be deflected by nucleus of the atom, and it is known as multiple Coulomb scattering (MCS). Both the protons and the nuclei are positive charged, therefore, their interactions are mostly Columbic. Highland's formula calculates the mean scattering angle θ [12, 13]:

$$\theta_0 = \frac{14.1 MeV}{pv} Z_p \sqrt{\frac{L}{L_R}} \left[1 + \frac{1}{9} \log_{10} \left(\frac{L}{L_R} \right) \right] rad \quad (4)$$

Where p = momentum of proton, $v = \beta c$ = proton velocity, L = target thickness, and L_R = radiation length of target material. The radiation length is the distance from which the energy of the radiation particles decreases due to radiation losses as much as $e^{-1} = (0.37)$ coefficient. In Fig 4, we compare the mean Coulomb scattering angle in terms of the proton energy at the range of $1 \leq E \text{ (MeV)} \leq 250$, for the injecting of different concentrations of GNPs in the BP.

Range calculations and range straggling

In this work, we use CSDA method to calculate the proton range. The CSDA range is obtained by integrating on the reciprocal of the total stopping power with respect to energy from E_0 to E_f where they are initial and final energy of proton, respectively, which is given by: [14]

$$CSDA R = \int_{E_f}^{E_0} \frac{dE}{S_{tot}} \quad (5)$$

In Fig. 5, the comparison of proton range variations versus proton energy at the range of $3 \leq E \text{ (MeV)} \leq 250$ without and with the injecting of GNPs in the breast tissue is depicted as a diagram. The loss of energy of an ion in matter is a statistical process and it is not definite and the Bethe's equation represents only mean energy loss. This variation was firstly obtained by Bohr, who introduced energy straggling (σ_E):

$$\frac{d\sigma_E^2(x)}{dx} \approx \frac{1}{4\pi\epsilon_0^2} e^4 \rho_e \quad (6)$$

where ρ_e = electron density. This is valid for energy loss that is large enough for maintaining Gaussian approximation but it is small enough when its energy can be assumed to be constant. Schulte et al. introduced the following differential equation: [15]

$$\frac{d\sigma_E^2(x)}{dx} = K(x) - 2 \frac{dS(E(x))}{dx} \sigma_E^2(x) \quad (7)$$

where $K(x)$ is represented as:

$$K(x) = z^2 \rho_e K \frac{1 - \frac{1}{2}\beta^2}{1 - \beta^2} \quad (8)$$

range straggling (σ_R), as a function of energy, is determined through the solution of the following equation:

$$\frac{d\sigma_R^2}{dx} = \frac{1}{S(E)} \frac{d\sigma_E^2(x)}{dx} \quad (9)$$

where $S(E)$ = the total mass stopping power.

Enhancement of radiotherapy by injecting GNPs into the tumor

In targeted cancer treatment, physicians use drugs that can better penetrate cancer cells to diagnose and treat [16,17]. For this purpose, GNPs are used as a photon active element simultaneously with PB irradiation. Radiation therapy by mixing NPs increases the number of photoelectrons in the tumor due to the presence of particles with a high atomic number. As the absorption of photoelectrons into the irradiated tumor increases, the absorbed dose of the tumor enhances. Experimental studies have shown that the size of NPs and how they are distributed in different organs are related with each other. The maximum accumulation of GNPs with diameters of 20-100 and 220 nm is in the liver and spleen, but NPs smaller than 10 nm in diameter were observed in most organs including kidney, heart, lung, brain, liver and spleen. NPs used in medicine are classified into two main groups. The first group of particles that contain organic molecules as the main building material and the second group that usually contain metals and minerals as the core [18,19], NPs (eg GNPs) are commonly used simultaneously with particle therapy to kill cancer cells due to their compatibility with the biological system and their low toxicity. One of the most important parameters of NPs is the choice of their synthesis method. Because the physical and chemical properties of the particles depend on it and is selected according to the type of coating agent, appropriate stabilizer and the desired size. In order to use GNPs biologically, their surface must be functionalized, which is called functionalization. The functionalization of NPs is done with the aim of smartening, insensitivity of the immune system and reducing toxicity in the body.

Depending on the application of functionalized NPs, different agents and compounds are used. For example, GNPs can be functionalized with polyethylene glycol to reduce toxicity, escape from the immune system and as a result, have a longer durability in the bloodstream (8). Another important feature of GNPs is their easy coupling with antibodies. Therefore, GNPs are injected into the patient's body in various ways, such as intravenous injection or injection at the tumor site. In a healthy tissue, endothelial cells have a regular arrangement and an impenetrable distance for NPs, but in a tumor tissue, the arrangement of endothelial cells is irregular and has large pores, which causes high NPs of gold permeability to tumor tissue. In this process, the antibodies first guide the NPs to the target cells and after attaching them to the target cells, they are irradiated. All cancer cells that interact with the NPs and are killed by the heat generated with the collision of electromagnetic waves caused by the radiation of a particle beam with GNPs.

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Authors' contributions

Conception and design of the study: SNH. Simulation: SNH,N.N. Analysis and interpretation of data: ZP, All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

Not applicable

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