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Article

Keywords:

Posted Date: August 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10567500/v1>

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Additional Declarations: No competing interests reported.

Predicting the Cell Survival Curve in Nanoparticle Enhanced Proton Therapy; A Geant4 Based Spectrometry

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Abstract: Through the present study, we demonstrate that, the reason of sensitization enhancement of proton therapy using metallic nanoparticles dominantly relies on proton deceleration by High-Z nanomaterials than the ejected secondary electron from their surfaces. It is emphasized that, in this study we discuss only on the direct effects on cell damage through the double-strand breaks (DSB)s induced by protons and not the variation of chemical effects or ROS which are considered as indirect effects with the lower impact in cell killing. Therefore, we have demonstrated that, the presence of metallic nanoparticles will lead to dramatically slowing the protons or increasing their linear energy transfer (LET) which causes the increase of induced direct damages.

To demonstrate the direct impact of nanoparticles on cell damage, we used the Geant4 Monte Carlo toolkit to assess the variation in induced DSBs as a function of proton LET in the presence of metallic nanoparticles.

The DSB yield was found to be directly correlated with proton energy spectrum. Analyzing the proton energy spectrum revealed that metallic nanoparticles cause a significant increase in DSB yield induced by protons while, the emitted secondary electrons with damage induction mostly through indirect effects, are not able to induce the DSB damages as much as of the protons.

To validate this mechanism, we modeled two previously reported experiments using Geant4. The DSB yields were calculated with and without nanoparticles, and the corresponding cell survival fraction curves were derived. Our simulated survival curves show strong agreement with the experimental reports, providing robust support for significant contribution of proton's LET enhancement than the ejected secondary electrons.

Introduction

This study aims to explain the misled analysis on the effect of High-Z nanoparticles (NP)s in proton therapy which, mostly has been interpreted according to the secondary electron ejected from NP's surfaces. This model successfully works for photons therapy in which, the use of High-Z nanoparticles (NP)s causes the ionization of NP's atoms by incident photons and the increase of secondary electron leads to the enhancement of radio-sensitization according to both the simulations and experimental results [1-5]. In proton therapy, the experimental observations show that, High-Z nanoparticles can increase the deposited dose significantly [6-20] but, the calculation of dose contributed only by the elevated number of secondary electrons leads to the results rather small or negligible in comparing with

experimental dose enhancement [7, 21-38]. This disagreement with experimental results suggests a fundamental piece of the puzzle is missing. In this regard, some authors have clearly indicated this discrepancy between simulation and experiment in NP-enhanced proton therapy as the evidence of the alternate mechanism dominating the dose enhancement [7, 13, 14, 20, 24, 25, 34] instead of electrons generation.

We have previously explained this puzzle through studying the (only) proton's spectra and the proton's dose profile with and without metallic NPs [39] showing that, the metallic NPs will cause both the spectra and deposited dose of protons. Though, the electron's contribution is obvious but, their significance in dose enhancement is smaller than protons as they contribute in cell damage indirectly.

When projectile's energy spectrum varies, the quantity of deposited dose and damage will be varied too, because of their dependencies on energy and the linear energy transfer (LET) as well [10, 40].

In present work, through the dependency of induced double strand breaks (DSB)s and proton energy spectra [41-43] we justified that, in NP-enhanced proton therapy, the key parameter is the changes in proton spectra in a cell's nucleus at Bragg's peak.

It is emphasized that, we have focused on direct damages induced by protons without considering the indirect effects from Reactive Oxygen Species (ROS). The agreement between our results with previous experiments can verify the proposed hypothesis of slowed-down protons by NPs as the reason of sensitization enhancement with greater significance than of the electrons.

In present investigation, using Geant4 Monte Carlo toolkit [44, 45], the proton's spectra inside a cell's nucleus located in middle of spread-out Bragg peak (SOBP) has been obtained with and without NPs.

Materials and Methods

In order to validate our mathematical formulation for predicting the cell survival fraction in proton therapy combined with nanoparticles, we have modeled some previously reported experiments and then, the predicted curves were compared to these reports. In this regard, the empirical data reported by Polf *et al* [16] and Brero *et al* [17] were used. In a microscopic point of view (as required for colonogenic assay), a small segment with depth of 2.2 mm within SOBP with and without NPs irradiated by protons as has been shown in Fig. 1 schematically. This depth is corresponding to the range of 13-15 MeV protons. The spherical cell and the nucleus diameters are 8 and 15 μm respectively. As it is seen, along the proton's trajectory there are the cells with NPs accumulated in their

cytoplasm. We have systematically demonstrated that, the NPs along the proton's path toward the stopping point will cause the increase of proton's energy loss when traversing the NPs. In this regard, the proton's spectra have been obtained with and without NPs inside the cell's nucleus at the given depth revealing that, the spectrum corresponding to NPs presence varies from the one without NPs. The changes in proton's spectrum leads to the change in number of the protons with specific LET and the induced damage as well. The yield of induced DSB which varies with variation of proton's spectrum has been calculated first. Then, the survival fraction (SF) curves in linear-quadratic (LQ) model for NPs presence have been derived and compared with mentioned experimental data. If the predicted SF curves corresponding to NP presence are aligned with the experimental curves, one can conclude that, the dominant mechanism in sensitization enhancement is the proton's LET variation by NP's atoms instead of low range secondary electrons production.

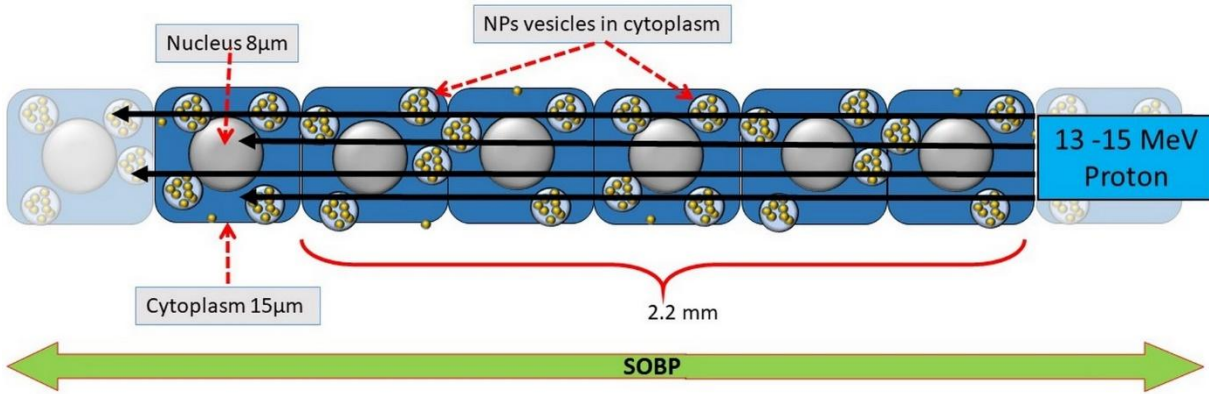


Fig. 1, a small segment of the whole SOBP region with depth of 2.2 mm has been irradiated by protons with different energies. The proton's spectra inside the nucleus of the cell at this depth was calculate with and without NP accumulation. The NPs specifications inside the cytoplasm were based on the Polf [16] and Brero [17] reports.

DSB Yield in term of Proton's Spectrum

This study analyzes the radiosensitization enhanced by NPs based on proton spectrometry. The protons energy spectrum demonstrates the number of protons as function of energy or LET, $fluence(LET_i)$. Also, according to LET-DSB relationship [40-42], the yield of induced DSBs is function of the proton's LET, $DSB_Yield(LET_i)$. Hence, the total number of DSBs induced by the protons with $fluence(LET_i)$ of i^{th} energy group can be calculated by Eq. 1;

$$Y = \sum_i [fluence(LET_i) \times DSB_Yield(LET_i)] \quad (1)$$

The yield of DSBs per proton, $DSB_Yield(LET_i)$, was extracted from Fig. 2 based on data reported by Friedland *et al* [40].

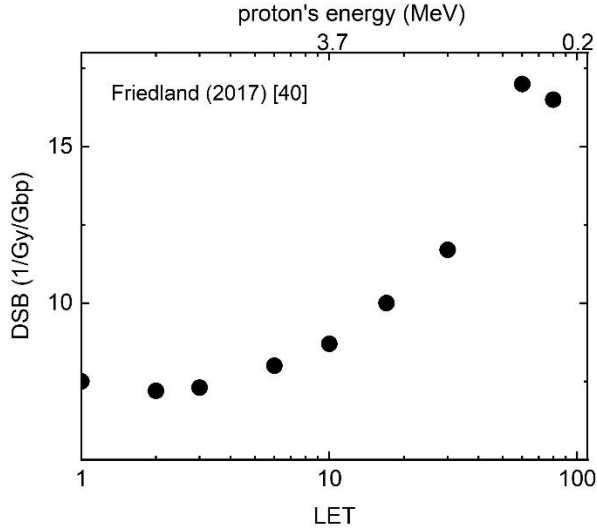


Fig. 2, DSB yield in terms of proton's LET according to Friedland [40] used in calculation of the total induced DSBs by Eq. 1.

Survival Fraction Prediction for NPs

Since yet, the survival fraction (SF) curve in NP-enhanced proton therapy could not be predicted by Monte Carlo due to the mentioned discrepancy. Here, the prediction of cell response in High-Z NPs combined with proton therapy can be achieved according to following descriptions. In linear-quadratic (LQ) model, the number of survived cells can be obtained by Eq. 2;

$$SF = e^{-\alpha D - \beta D^2} \quad (2)$$

Where, α and β are fitting parameters. Wenjing *et al* [46] has defined a relationship between SF and the induced double strand breaks (DSB)s in cell nucleus. Accordingly, the fitting parameters of α and β can be obtained in terms of N , the average number of induced DSBs per cell, $N = Y \times D$, in where, Y is average number of induced DSBs per cell per dose (Gy) and D is dose (Gy).

In Wenjing report, the survival fraction is defined by Eq. 3 where, C_1 and C_2 are constants;

$$SF = e^{-C_1(N) - C_2(N)^2} = e^{-C_1(YD) - C_2(YD)^2} \quad (3)$$

Therefore, from the Eq. 2 and Eq. 3, α and β parameters can be derived as;

$$\alpha = C_1 \times Y \quad \& \quad \beta = C_2 \times (Y)^2 \quad (4)$$

The fitting parameters corresponding to the *control* treatment (without NPs) and with NPs are denoted, respectively;

$$\alpha_{control} = C_1 \times Y_{control} \quad \& \quad \beta_{control} = C_2 \times (Y_{control})^2 \quad (5)$$

and

$$\alpha_{NP} = C_1 \times Y_{NP} \quad \& \quad \beta_{NP} = C_2 \times Y_{NP}^2 \quad (6)$$

finding C_1 and C_2 in Eq. 5 and substituting in Eq. 6, we have;

$$\alpha_{NP} = \alpha_{control} \times \left(\frac{Y_{NP}}{Y_{control}}\right) \quad \& \quad \beta_{NP} = \beta_{control} \times \left(\frac{Y_{NP}}{Y_{control}}\right)^2 \quad (7)$$

Finally, the survival fraction, Eq. 2, corresponding to NPs is $SF = e^{-\alpha_{NP}D - \beta_{NP}D^2}$ and can be written with *control* based parameters;

$$SF = e^{-\left[\alpha_{control} \times D \times \left(\frac{Y_{NP}}{Y_{control}}\right)\right] - \left[\beta_{control} D^2 \left(\frac{Y_{NP}}{Y_{control}}\right)^2\right]} \quad (8)$$

Eq. 8, potentially predicts the colonogenic assay in NP's enhanced proton therapy according to control-based fitting parameters, $\alpha_{control}$ and $\beta_{control}$, and the ratio of DSB yield with NPs on without NPs. By modeling the two previous experiments and comparing the predicted SF curves with experimental SF curves, we can justify the hypothesis of LET elevation through proton's slowed-down or deceleration by NPs as the dominant mechanism in NP-enhanced proton therapy.

In present geant4 simulation, the cut-values were 1 nm [21, 34] with 10^7 event histories to achieve the results with error less than 5 %. The protons elastic and inelastic interactions were simulated by *G4HadronElasticPhysicsHP*, *G4HadronPhysicsQGSP_BIC_HP* and also, *G4EmStandardPhysics_option3* for electromagnetic interactions.

The elevation of radiation LET by metallic NPs has been previously discussed for proton beam therapy [47, 48] and also for photon therapy [49]. Here, we have demonstrated the impact of NPs on cell damage through this mechanism. Two previous experiments by proton beam and metallic NPs were modeled in present study and the proton's spectrum inside a typical within SOBP region was simulated to investigate the variation in proton's spectrum due to presence of the gold and Iron NPs. The variation of proton's energy spectrum means the changes in number of the protons having the specific LET. According to the relation between LET and DSB yield [40-42], when the energy spectrum varies, the number of induced DSB as function of LET or energy varies too.

Results

Figs. 3a and 3b depict the energy spectra corresponding to protons interactions with and without GNPs and FeNPs according to Polf's [16] and Brero's [17] experiments.

Our Monte Carlo simulations revealed a significant localized increase in LET in cell's nucleus and hence, the DSB induction when primary protons interacting with metallic NPs. In these figures, the proton's energy spectra are presented in red symbols showing the changes in fluence due to NPs. The DSB yield corresponding to each energy group; $DSB_Yield(LET_i)$ was quantified using DSB-LET relation in Fig. 2 reported by Friedland *et al* [40]. The production of $DSB_Yield(LET_i) \times fluence(LET_i)$ for each energy group are depicted in these figures by black symbols. It is shown that, in presence of GNPs and FeNPs, the total number of induced DSBs are increased significantly. This is the evidence of enhancement in direct DNA damage when metallic NPs are added to proton therapy. However, to confirm and justify that, the LET elevation in Fig. 3 is the reason of radiosensitization enhancement in NP-proton therapy, we have predicted the cell response by colonogenic assay to compare with empirical data.

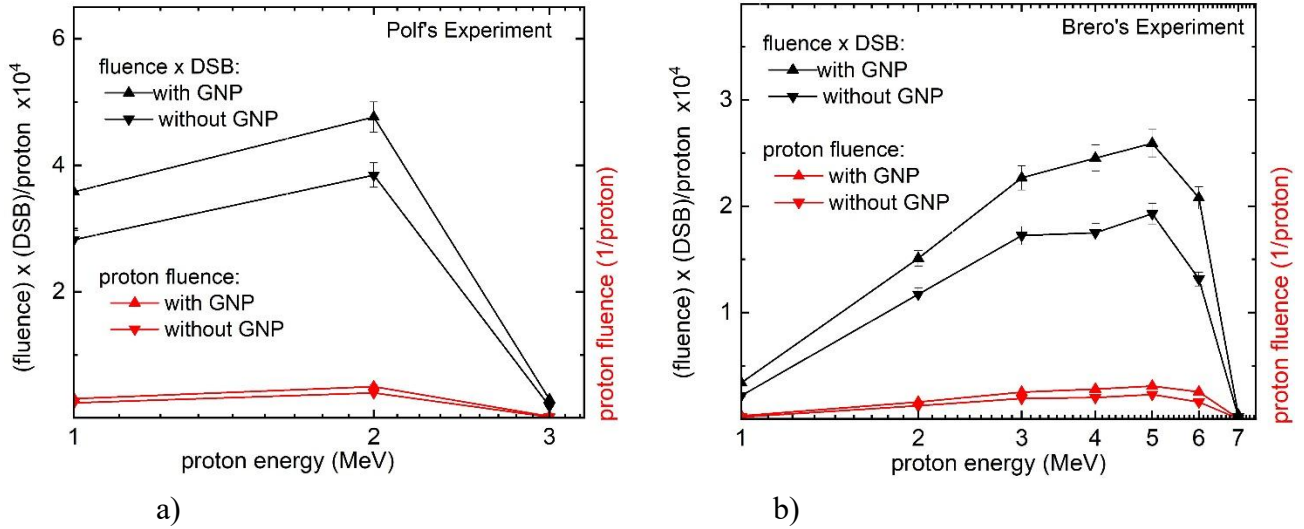


Fig. 3, the calculated proton spectrum and corresponding DSB yield in terms of proton energy related to with and without NPs according to modeling a) Polf et al [16] experiment using GNPs and b) Brero et al [17] using FeNPs. The error bars show 5 % deviations.

Colonogenic Assay Simulation Results

Table 1, shows (Y_{NP}) and $(Y_{control})$ as the total yield of induced DSBs corresponding to with and without NPs quantified by Eq. 1. Then, the ratio of $(\frac{Y_{NP}}{Y_{control}})$ are 1.259 and 1.387 based on modeling

the Polf's and Breros's experiments respectively. This table also, shows the α_{NP} and β_{NP} parameters obtained by Eq. 7. The survival fraction (SF) curves related to GNP and FeNP treatment have been predicted by Eq. 8 and the corresponding curves are demonstrated in Fig. 4a and 4b in dashed lines compared with the reported experimental curves in black solid lines corresponding to NP treated. The treatment without NPs are presented in blue symbols. There is a good agreement between obtained SF curves by simulation and the in-vitro reported data for both the experiments. For Polf's report, the fitting parameters were not provided by the authors and in present study, they were extracted manually as it is in Table 1. From this figure, the hypothesis of proton slowed-down mechanism or deceleration by metallic NPs can be justified as the mechanism dominating the proton-enhanced NP treatment.

Table 1. the calculated total induced DSB yield with and without NPs represented by $Y_{control}$ and Y_{NP} respectively. The ratio of $(Y_{control}/Y_{NP})$ also is quantified to calculate the NP related values of α and β parameters in present study.

Reference Experiment	Eq. (1):		$(\frac{Y_{NP}}{Y_{control}})$	Eq. (7):	
	$(Y_{control})$	(Y_{NP})		$\alpha_{NP} = \alpha_{control} \times (\frac{Y_{NP}}{Y_{control}})$	$\beta_{NP} = \beta_{control} \times (\frac{Y_{NP}}{Y_{control}})$
Polf [16]	68645	86440	1.259	$(0.47 \pm 0.05) \times (1.259)$	$(0.011 \pm 0.01) \times (1.259)$
Brero [17]	81269	112750	1.387	$(0.63 \pm 0.05) \times (1.387)$	$(0.015 \pm 0.01) \times (1.387)$

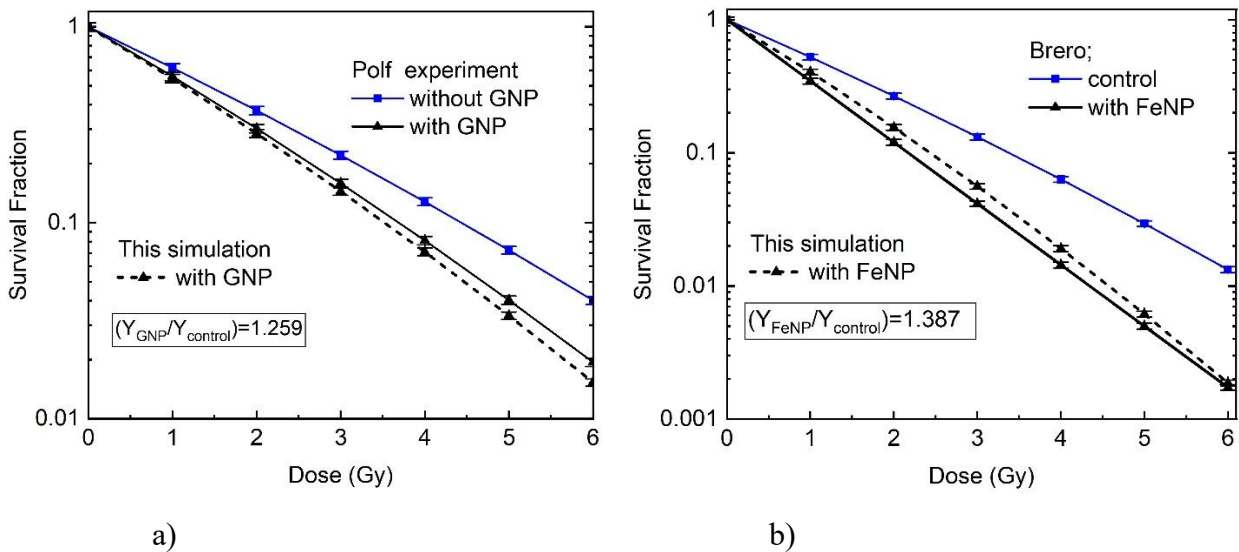


Fig. 4, the survival fraction curves according to predicted by present simulation and the reported data by a) Polf et al [16] and b) Brero et al [17]. The error bars show 5 % deviations.

Discussion

Due to discrepancy between in-vitro observations and simulation in using metallic NPs in proton therapy, some researchers have strongly indicated that, the mechanism contributing to metallic NP-enhanced proton therapy remains incompletely understood and must be fully elucidated [7, 13, 14, 20, 24, 25, 34]. In following discussion, we explain that, different from photon therapy with NPs that, sensitization enhancement dominated by electrons, in proton therapy, the sensitization is enhanced through elevation of the projectile's LET because of the NP's higher stopping power.

Since, both photon and proton inelastic interactions involve ionization and excitation of atoms of medium leading to secondary electrons and δ -ray generation, the scientific community has thus logically, but incorrectly, applied the established photon-based model to proton therapy without fully accounting for alternate, proton-specific mechanisms.

X-rays or gamma-ray photons, damage DNA indirectly and exclusively through the kinetic energy of ejected secondary electrons while protons, directly induces DNA damages. When protons are slowed down by losing energy to inelastic interactions, their LET will be elevated leading to RBE enhancement. From the Bethe-Bloch formula, $(\frac{dE}{dx} \propto Z_{medium})$ [50], the presence of High-Z nanoparticles will cause the greater energy loss, the electronic stopping power and therefore, the elevated LETs leading to the increase in damage induction. The resulting LET elevation is a mechanism of far greater significance for cell damage than the contribution from secondary electrons alone.

Furthermore, our findings suggest an important consideration for clinical translation: even a lower concentration of NPs accumulated in healthy surrounding tissues could alter the local proton energy spectrum. This effect must be carefully evaluated in future studies and incorporated into treatment planning systems to ensure the safe application of metallic nanoparticles in proton therapy.

Conclusion

Through the studying the variation of proton energy spectrum in presence of metallic nanoparticles as the LET elevation mechanism, we explained the reason that, radio-sensitization in proton therapy is enhanced while, the previous old-standing hypothesis of secondary electron couldn't explain it and led to a paradox between in-vitro observations and the simulation results.

Also, for the first time, we introduced a method to predict the survival fraction curves in nanoparticle-enhanced proton therapy.

Acknowledgement

We hereby appreciate Physics department of Imam Khomeini International University for their kind support.

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Funding: No funding was received for conducting this study.

Conflicts of interest/Competing interests: The authors of the present work declare no competing financial interests.

Availability of data and material: The datasets generated and/or analyzed during the current study are available from the corresponding author.

Code availability: All simulations and the related programs of GEANT4 code, are available from the corresponding author.

Authors' contributions: Farshid Tabbakh and Sama Molaei conducted the experiment(s) and results, Farshid Tabbakh, Ahmad Mehramiz and Nader Morshedian have performed the discussions. All authors have reviewed the manuscript.

In the present study no human (or animal) tissue was involved.