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Radiosensitization Effect of the Gold Nanoparticle in the Cell Simulated with NASIC Code

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Abstract - *Gold nanoparticle (GNP) can be used as a radiation sensitizer in radiotherapy, and many Monte Carlo simulation studies have focused on this issue. A nanodosimetry biophysics Monte Carlo code NASIC was used in this work to study both the physical and biological radiosensitization effect of GNP in the cell environment under the irradiation of X-ray. GNP-cell models were built in the simulation with single GNP in the nucleus center or four different ideal distributions of multiple GNPs. The influence of X-ray energy, GNP size and distribution on the energy deposition, DSB number and cell survival fraction were studied. The results show that the enhancement effect of energy deposition occurs in the vicinity (~2 μm) of GNP. The variation trend of the total energy deposition in the nucleus, DSB number and cell survival fraction with X-ray energy and GNP diameter are similar, but the enhancement factors decrease with the largest values as 1.47, 1.32 and 1.14 respectively. The radiosensitization effect with 40 keV X-ray energy, 100 nm GNP diameter and GNPs distributing on the nucleus surface have advantage over other parameter values. The study results can help to understand the mechanism of radiosensitization effect and give advices on GNP clinical application in the radiotherapy.*

I. INTRODUCTION

The major concern of radiotherapy is increasing the tumor control probability combined with decreasing normal tissue complications, to increase the therapy gain ratio. Other than the intensity modulated radiotherapy, heavy ion radiotherapy, etc., using the radiosensitizer is also an effective way. Since high atomic number materials have more interaction probability with the X-ray, gold is proved to be a radiosensitizer in radiation therapy [1]. X-ray will deposit more energy in the tissues containing the GNP, which leads to more radiation damages in the cell and induces the radiosensitization effect. Besides, GNPs can cumulate in the tumor cell through active and passive ways, and is biocompatible, economical to synthesize and so on [2]. In addition to the radiobiology experiment, Monte Carlo simulation also provides an effective way to study the radiosensitization effect of GNP [3-8], and many general Monte Carlo simulation codes, such as MCNP, EGS, GEANT4 and PENELOPE, were used in the study with different irradiation conditions and models. However, most of these simulation studies focused on the enhancement effect of physical quantities, such as the energy deposition, dose, etc., and few of them paid attention to the enhancement effect of biological quantities, such as DNA damage, cell survival fraction, etc.

As a biological end point reflecting the radiotherapy effect, cell survival fraction is an important object to evaluate the radiosensitization effect. As the mid biological effect, radiation damages of the cell, especially the damage of DNA containing the genetic material, may induce the cell death and can also be regarded as an evaluation object. What's more, all the biological effects are based on the physical interaction between the radiation and biological medium, thus the correlative physical quantities should also be analyzed in the study of GNP radiosensitization effect. General Monte Carlo codes can only simulate the particle transportation in millimeter and micrometer scales, and they are unable to simulate the physical transportation in nanometer scale and the subsequent chemical and biological interactions. Therefore, the nanodosimetry biophysics Monte Carlo code is needed when studying the GNP radiosensitization effect in these three aspects at the same time. In this paper, using a nanodosimetry biophysics Monte Carlo code NASIC and a biological target model with atomic resolution, radiation sensitization effect of the GNP within the cellular environment under the irradiation of X-ray was studied, including both physical quantities and biological responses. This helps to understand the mechanism of enhancement effect, estimate radiation biological responses in a cell and give advices on GNP clinical application in the radiotherapy.

II. DESCRIPTION OF THE ACTUAL WORK

1. Nanodosimetry Biophysics Monte Carlo Simulation Code - NASIC

In order to simulate the whole interaction process of radiation in organism, a nanodosimetry biophysics Monte Carlo code was developed and named as NASIC [9-11]. Generally, there are 3 stages in the interaction process of radiation in organism: physical stage, chemical stage and biological stage. Accordingly, NASIC includes physical

module, pre-chemical module, chemical module, geometric module, DNA damage module, DNA damage repair module and cell death module (fig. 1). The physical module records the track structure of radiation using a step-by-step method, and the coordinates, energy deposition, interaction type of every step are stored. In the pre-chemical module, the ionized and excited water molecules undergo certain dissociation and thermalization processes, producing some radiolytic chemical species. Besides, the subexcitation electrons are thermalized into hydrated electrons. These radiolytic radical species diffuse and react with each other in the chemical module.

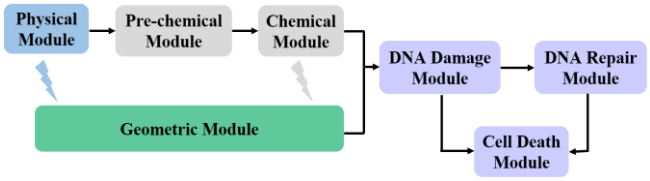


Fig. 1. Module structure of NASIC.

In the geometric module, a detailed atomic model of 11 μm human interphase spherical nucleus was built, filled with 46 chromatins plus 2 nucleoli. The atomic model includes the double helix, nucleosome, chromatin fiber and nucleus, and the total genomic length is about 6.2 Giga base pairs (fig. 2).

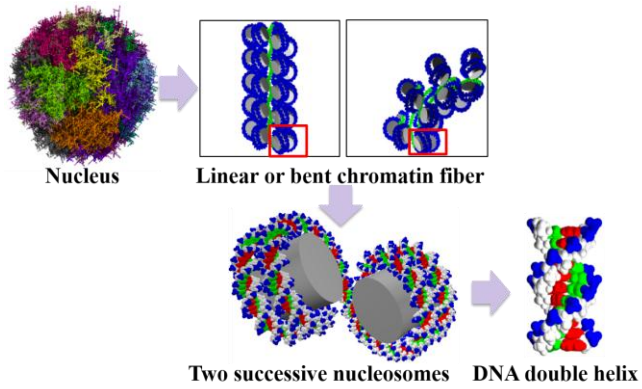


Fig. 2. The atomic nucleus model in NASIC.

In the DNA damage module, the direct DNA damage which is induced by the radiation directly interacting with DNA molecule in the inelastic collision process, and the indirect DNA damage which is induced by the free radical species produced after the radiation interacting with water molecule near the DNA are simulated. The distribution of DNA single strand break (SSB), double strand break (DSB) and base damage (BD) can be obtained. The DNA damage repair module is currently being developed.

In the cell death module, a relationship between the DSB yield and cell death was established. Based on the famous linear-quadratic model of cell survival[12-13], the sum of αD and βD^2 was replaced by the total DSB number calculated with NASIC corresponding to the dose D, and then this was combined with the target theory[14] to get the model equation in NASIC (equation 1). Using the experimental cell survival fraction data and the DSB yield calculated by NASIC, the cell specific parameter q and p can be determined.

$$S = q \cdot \exp\left[- p \cdot DSB\right] \quad (1)$$

2. GNP- Cell Models

In this study, two concentric spheres represented a simple cell model. The inner sphere with 11 μm diameter represented the nucleus volume which contained the atomic DNA model built in NASIC, and the outer sphere with 30 μm diameter represented the cell volume. The cell region other than the nucleus was defined as the cytoplasm. The cell composition and the surrounding medium were defined as liquid water with density of 1.0 g cm^{-3}.

The GNP diameter was set as 2 nm, 14 nm, 50 nm, 74 nm and 100 nm in the simulation, referring to the GNP sizes usually chosen in the experiment [15-16]. As for the single GNP simulation, the GNP was placed in the center of the nucleus (fig. 3(a)). In the multiple GNPs simulation, four ideal GNP distributions in the cell were performed based on the experimental observation of GNPs movement in the cell [17-20] (fig. 3(b) ~ 3(e)): GNP randomly distributed on the nucleus surface, on a virtual surface in the cytoplasm (20 μm diameter), on the cell surface, and randomly within the cytoplasm. The kinetic process of cell intake and transport of GNPs were not considered in this study, and the number of GNPs in the multiple GNPs simulation was set as 1000.

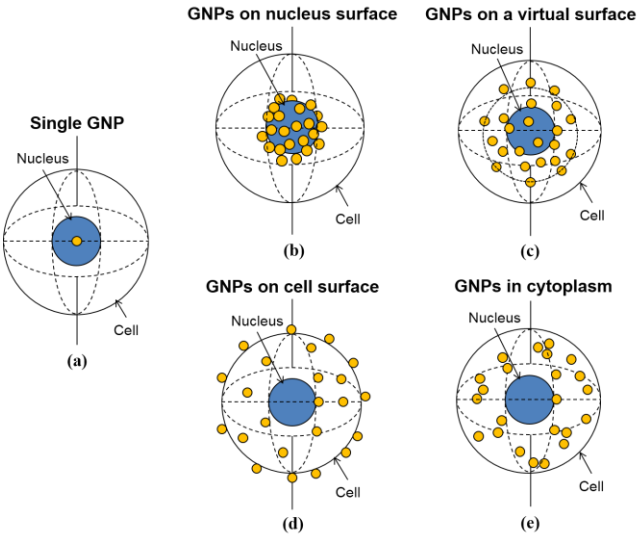


Fig. 3. GNP distributions in GNP-cell models: (a) single GNP in the nucleus center; (b) GNPs on the nucleus surface;

(c) GNPs on a virtual surface in the cytoplasm; (d) GNPs on the cell surface; (e) GNPs randomly within the cytoplasm.

3. X-ray Source and Physical Transport

Since the actually used X-ray spectrums are influenced by the machine structure, target material and so on, monoenergetic X-rays with seven energies as 20 keV, 40 keV, 60 keV, 80 keV, 100 keV, 150 keV and 200 keV were used in this study. The parallel X-rays were emitted from a circular plane along the axis connecting the center of the source plane and the cell. In the single GNP simulation, the distance from the source center to the cell center was 20 μm, and the diameter of the source plane was 1 μm. In the multiple GNPs simulation, the distance between the two centers was 430 μm, and the diameter of the source plane was 35 μm.

All the secondary electrons produced by the X-ray interacting with the liquid water or the gold were transported with step-by-step method until the energy was lower than the cutoff energy. The cutoff energy for the X-ray was set as 50 eV, and for the electron was 7.4 eV.

4. Radiosensitization Effect Simulated with NASIC Code

The simulation study of GNP radiosensitization effect was divided into two parts as physical and biological radiosensitization effect. The physical radiosensitization effect was for the physical quantities which can be directly obtained from the track structure of the radiation, including energy deposition in the nucleus and cell. The biological radiosensitization effect was for the biological quantities such as the DSB number and cell survival fraction, which further needed the subsequent chemical and biological simulation and calculation.

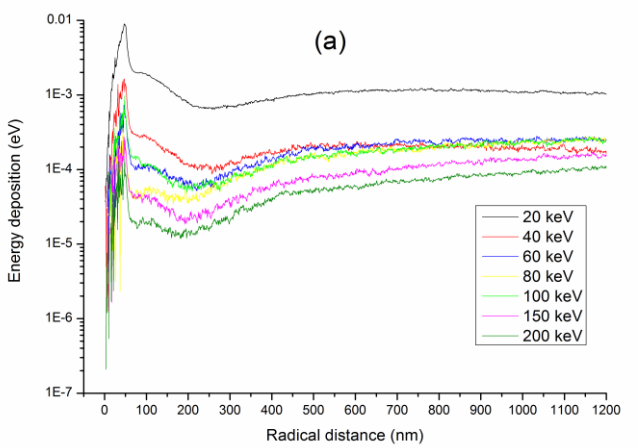
Firstly, the distribution of energy deposition in the cell for the single GNP situation was simulated with different GNP diameters and X-ray energies, to study the influence of these two factors on the physical radiosensitization effect. Then, the energy deposition distributions for multiple GNPs with the four different distributions were simulated to study the influence of the GNPs distribution. For these simulation, the cell was divided into 15000 shells with 1 nm thickness, and the energy deposition in each shell was counted to obtain the radical distribution of energy deposition in the cell. As for the multiple GNPs on the nucleus surface, the physical radiosensitization effect of energy deposition in the nucleus, and the biological radiosensitization effect of the DSB number and cell survival fraction with different GNP diameters and X-ray energies were also studied.

In order to quantitatively evaluate the GNP radiosensitization effect, the enhancement factor (EF) was defined as the ratio of a certain quantity under the same condition but with and without the GNP. Thus a set of simulations without GNP were also carried out. In the single GNP simulation, the total number of X-rays ranged from 1×10^7 to 2×10^8, to control the relative standard error of energy deposition in the GNP volume less than 10%. In the multiple GNPs situation, the total number of X-rays ranged from 5.8×10^7 to 4.8×10^8, to control the relative standard error of energy deposition in the nucleus less than 10%.

III. RESULTS

1. Physical Radiosensitization Effect

As for the single GNP situation, fig. 4 and fig. 5 show the radical distribution of energy deposition and enhancement factor EF_{Dep} in the cell under the irradiation of X-rays with different energies and with 100 nm GNP diameter, and under the irradiation of 20 keV X-rays with different GNP diameters, respectively. It can be seen that the absolute value of energy deposition is relatively high in the GNP volume and rapidly decreases with radical distance from the GNP surface, which induces a sharp peak near the GNP surface. The radical distance of the region with obvious energy deposition increase is less than 300 nm. When the X-ray energy is fixed as 20 keV, the energy deposition increases with the GNP diameter, and 100 nm GNP diameter induces the most energy deposition. And the X-ray with 20 keV energy has an obvious advantage compared with the other energies when the GNP size is 100 nm diameter. It shows that the largest EF_{Dep} occurs near the GNP surface about 100 ~1000, and EF_{Dep} rapidly decreases to less than 10 at the radical distance about several hundred nanometers, and then slowly decreases until stable near 1. The enhancement effect can be seen in the radical distance less than about 2000 nm with EF_{Dep} lager than 1. As for the X-ray energy and GNP size, the largest EF_{Dep} occurs in 20 keV energy and 100 nm diameter respectively, which is the same as the absolute value of energy deposition.



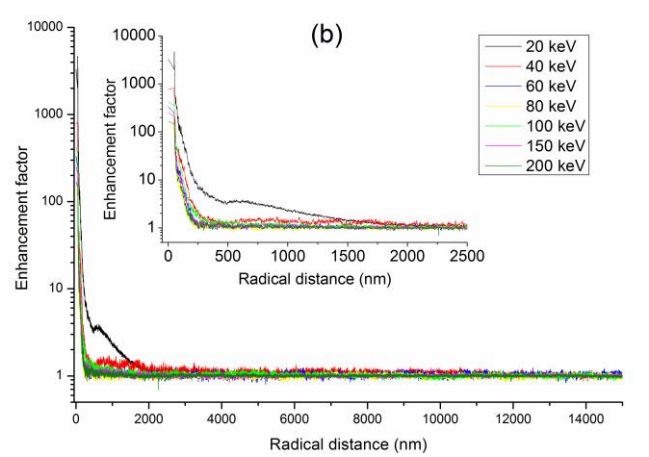


Fig. 4. Radical distribution of energy deposition (a) and EF_{Dep} (b) with 100 nm GNP diameter and different X-ray energies.

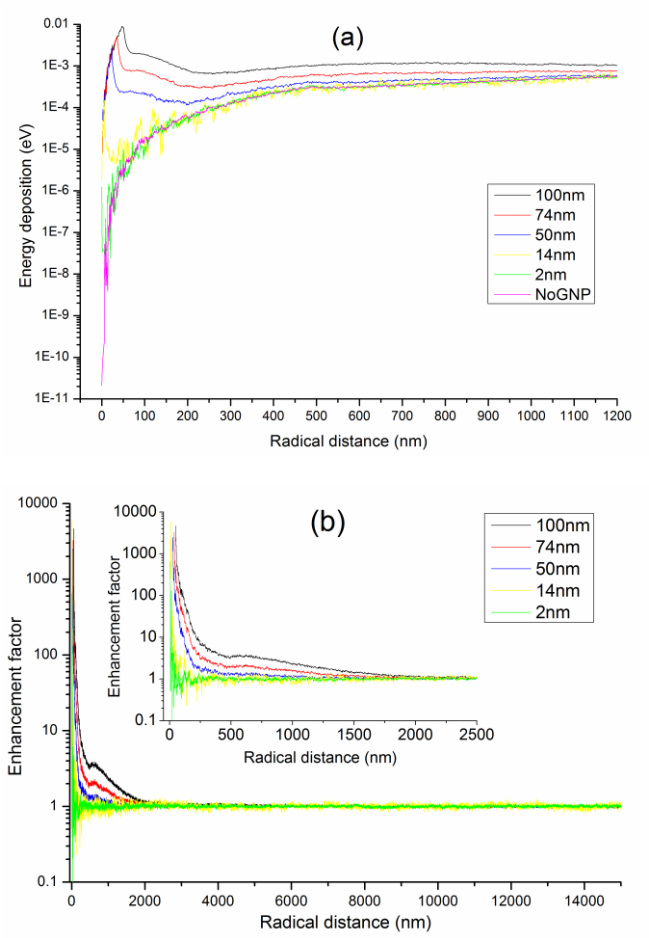


Fig. 5. Radical distribution of energy deposition (a) and EF_{Dep} (b) with 20 keV X-ray energy and different GNP diameters.

Fig. 6 shows the radical distribution of energy deposition and enhancement factor EF_{Dep} for the multiple GNPs situation with different distributions. As for the (b), (c) and (d) distributions, the energy depositions increase greatly in 1 μm around the GNP shell, and then go slowly back to the "No GNP" level within about 2~3 μm. The curve of the (d) distribution is relatively flat and only slightly above the "No GNP" level. The largest EF_{Dep} is about 10 for (b) distribution, about 4 for (c) distribution, and falls in to the range of 1~2 for (d) and (e) distributions.

In brief, the most obvious GNP physical radiosensitization effect is induced by 20 keV X-ray energy, 100 nm GNP diameter and nucleus surface GNPs distribution.

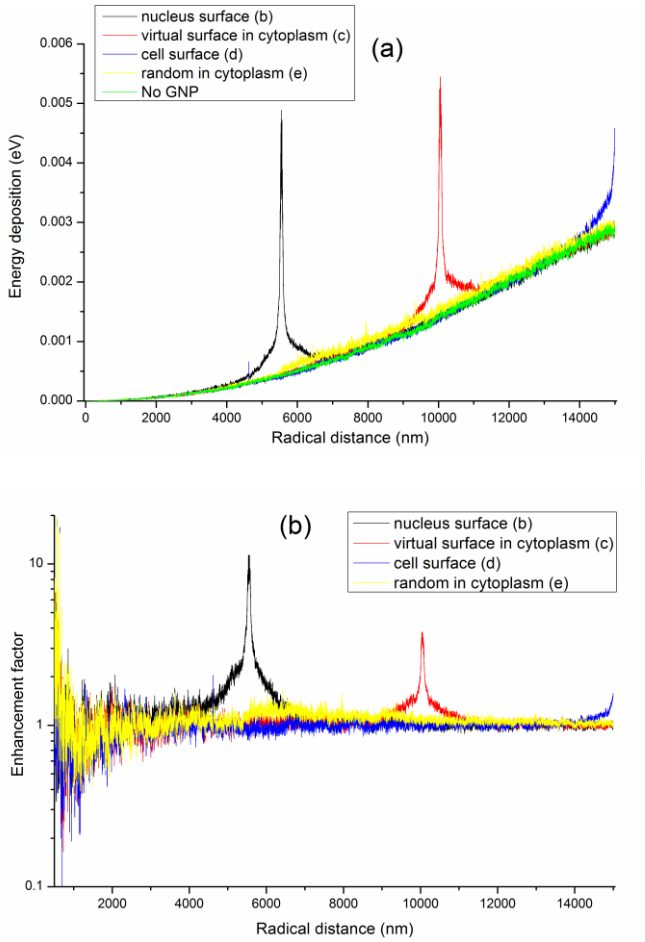


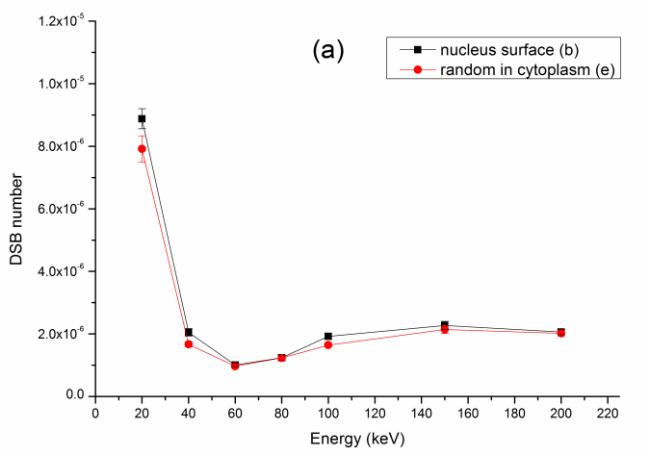
Fig. 6. Radical distribution of energy deposition (a) and EF_{Dep} (b) for different GNPs distributions with 100 nm GNP diameter under the irradiation of 20 keV X-ray.

According to the time evolution of the interaction process of radiation and the biological medium, physical interaction is the front input of the biological effect. The physical radiosensitization effect is mainly attribute to the positive correlation between the cross section of the

photoelectric effect and the atomic number Z. Thus the number of the interaction of X-ray with high Z material gold is much larger than with the liquid water in the same volume, and more secondary electrons are produced. The energy of secondary electrons are finally deposited in the biological medium by the inelastic collision process, which increases the total energy deposition and induces the physical radiosensitization effect. As for the single GNP situation, the obvious physical radiosensitization effect is occurs less than about 300 nm radical distance, and for the multiple GNPs situation is about 2 μm from the GNP shell, which are all near the GNP region. This is because each photoelectric effect or Compton scattering will produce a relatively high energy photoelectron or recoil electron, and a series of low energy auger electrons with short range. Though the range of auger electrons in the water are about hundreds nanometers, the number is much larger than the photoelectron or recoil electron, which lead to the obvious enhancement effect of energy deposition near the GNP surface. And the photoelectron or recoil electron with relatively high energy mainly induces the enhancement effect in a greater distance about a few micrometers. The short range of the secondary electron limits the obvious physical radiosensitization effect only near the GNP.

2. Biological Radiosensitization Effect

Since the (c) and (d) distributions of the multiple GNPs have little influence on the energy deposition in the nucleus, the DSB number and enhancement factor EF_{DSB} only for the (b) and (e) distributions varying with the X-ray energy and GNP diameter were simulated, which are shown in fig.7 and 8. It can be seen that the (b) distribution can induce more obvious biological radiosensitization effect of the DSB number in the nucleus.



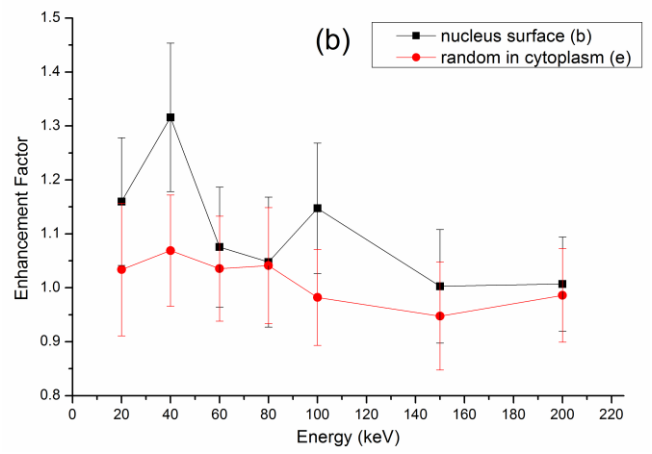
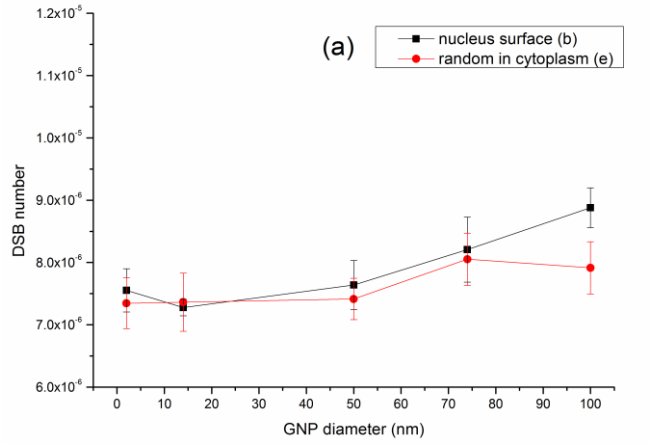


Fig. 7. Average number of DSB induced per X-ray (a) and EF_{DSB} (b) for the (b) and (e) GNPs distributions with 100 nm GNP diameter.



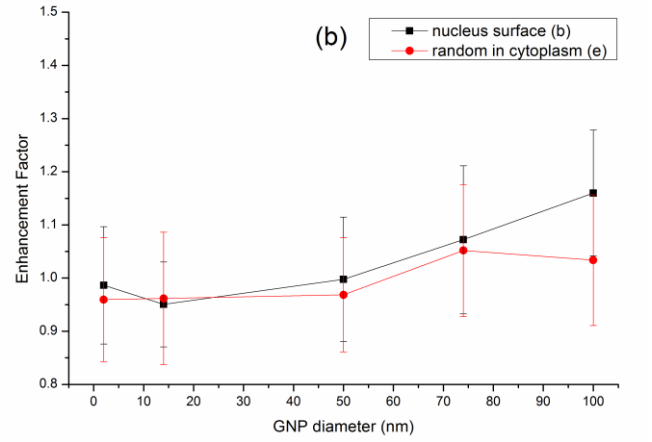


Fig. 8. Average number of DSB induced per X-ray (a) and EF_{DSB} (b) for the (b) and (e) GNPs distributions irradiated with 20 keV X-ray.

As for the multiple GNPs distributing on the nucleus surface, the enhancement factor of energy deposition in the nucleus EF_{Dep}, the DSB number EF_{DSB}, and the cell survival fraction under the 1 Gy dose level EF_{SF} are compared in fig. 9. It can be seen that though the absolute value of DSB number under the irradiation of 20 keV energy is the largest, the EF_{DSB} and EF_{SF} of 40 keV are the largest. And the biological radiosensitization effect of the DSB number and cell survival fraction increase with the GNP size, which is the same as the physical radiosensitization effect of energy deposition. In general, the influence of X-ray energy and GNP diameter on the physical enhancement effect are similar to the influence on biological enhancement effects, but the degrees are different. The EF of energy deposition in nucleus is often larger than the EF of DSB number, and the EF of cell survival fraction is often the smallest, with corresponding largest EF values as 1.55, 1.32 and 1.14 respectively.

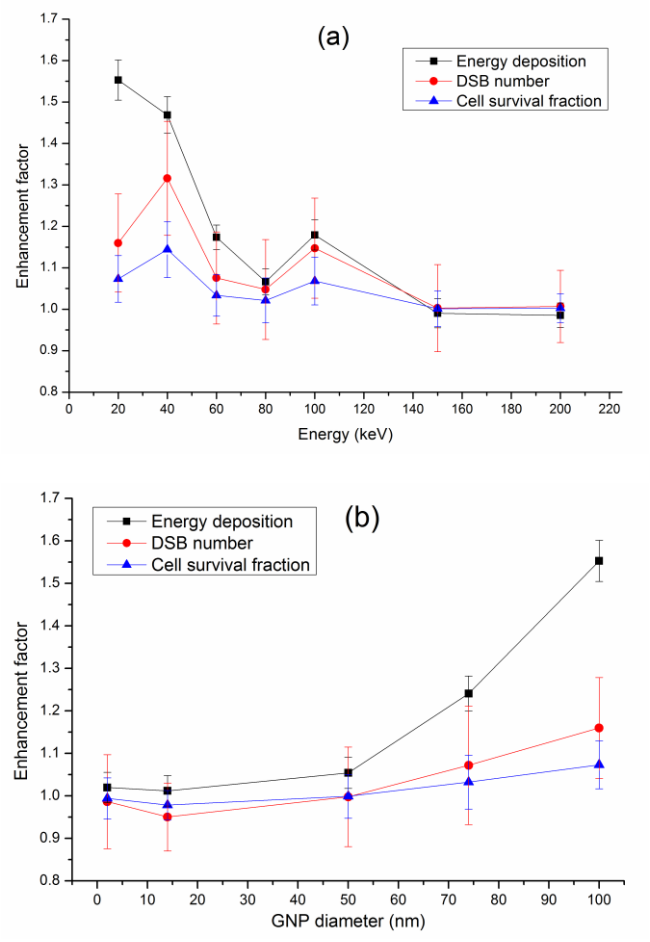


Fig. 9. Enhancement factor of energy deposition in nucleus, DSB number and cell survival fraction with GNPs distributing on the nucleus surface: (a) GNPs with 100 nm diameter irradiated with various X-ray energies; (b) GNPs with various diameters irradiated with 20 keV X-ray.

The physical interaction between the radiation and biological medium may induce the DNA strand break in direct or indirect way, and many DSBs may induce cell death if they are not correctly repaired in time. The GNP in the cell greatly increases the probability of photoelectric effect or Compton scattering, and the number of secondary electrons which deposit energy by inelastic collision and produce free radical species. The more secondary electrons and radical species interact with the DNA molecule in the nucleus, the more DSBs and more complex DNA damage will be induced, and then the probability of cell death increases. Therefore, the enhancement effect of energy deposition in the nucleus, DSB number and cell survival fraction have the similar variation trend with the X-ray energy or GNP size.

As for $EF_{Dep}>EF_{DSB}>EF_{SF}$, it is related to the distribution of energy deposition in the cell, the distribution of DNA in the nucleus and the biological response process from DSB to cell death. When the X-ray interacts with the GNP near the nucleus surface, the produced secondary electrons will deposit more energy and produce more radical species in the nucleus. Because of the short range of these electrons, the most of the increased energy deposition and radical species in the nucleus only distribute near the nucleus surface, and only part of them effectively interact with the DNA molecule, which lead to the EF_{DSB} less than EF_{Dep}. Besides, a part of DSBs can be correctly repaired via the cell DNA damage repair process, and only the rest unrepaired or mistakenly repaired DSBs may induce the cell death, and thus the EF_{SF} is further decreased.

IV. CONCLUSIONS

In this paper, the simulation study of GNP radiosensitization effect in the cell environment under the irradiation of monoenergetic X-ray was carried out with nanodosimetry biophysics Monte Carlo code NASIC, at the physical level about the energy deposition and biological level about the DSB number and cell survival fraction. The results show that enhancement effect of energy deposition can be observed in 2 μm radical distance around the GNP, which increases with GNP size and is largest for 20 keV X-ray energy. When GNPs distributed on the nucleus surface and the nucleus is regarded as the biological target, the enhancement effect of energy deposition in the nucleus, DSB number and cell survival fraction have the similar variation trend with X-ray energy and GNP size, but $EF_{Dep}>EF_{DSB}>EF_{SF}$. In present study, the radiosensitization effect with 40 keV X-ray energy, 100 nm GNP diameter and GNPs distributing on the nucleus surface are relatively more effective conditions for both physical and biological radiosensitization effect, and EF_{Dep}, EF_{DSB}, EF_{SF} are 1.47, 1.32 and 1.14 respectively.

According to the study results, if a stronger biological sensitization effect is required in the GNP cell experiment,

X-ray spectra should distribute more within the range of 20 ~ 60 keV, and the number of GNPs entering cell and staying close to or even entering the nucleus should be as much as possible. Since some ideal parameters and conditions were used in the present simulation, the real X-ray source used in radiotherapy and biokinetics distribution of GNPs in the cell environment need to be considered in further study.

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