Evaluation of Gold Nanoparticles Radio Sensitization Effect in Radiation Therapy of Cancer

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Evaluation of Gold Nanoparticles Radio Sensitization Effect in Radiation Therapy of Cancer

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Abstract In radiotherapy, ionizing radiations such as X-rays, gamma, high-energy particles are widely using for the treatment of cancer tumors in solid form. Unfortunately, ionizing radiations are not capable of detecting cancer cells from healthy cells. Therefore, healthy tissue hurts due to radiotherapy for eradicating the cancer cells. Improved radiotherapy outcomes can be achieved by employing ion beams due to the characteristic energy deposition curve which culminates in a localized, high radiation dose. Some studies indicated energy dependency of dose enhancement effect, and the others have studied the gold nanoparticle (GNP) size effect in association with photon energy. However, in some aspects of GNP-based radiotherapy the results of recent studies do not seem very conclusive in spite of relative agreement on the basic physical interaction of photoelectric between GNPs and low energy photons. The purpose of the current paper was to assess the current status of gold nanoparticles applications in radiation therapy. In this review, we summarized the mechanisms of action of radiation therapy with photons and ions in the presence and absence of nanoparticles, as well as the influence of some of the core and coating design parameters of nanoparticles on their radio sensitization capabilities.

Keywords Gold Nanoparticle, Radiation Therapy, Radio Sensitization, Cancer

1. Introduction

Nanoparticles are defined as particles in size 1 to 100 nm. However, in some studies, even particles up to 1 micrometer are considered nanoparticles [1, 2]. In targeted treatments of cancer, pharmaceuticals that can penetrate better in cancer cells are used for treatment and diagnosis. The distribution of nanoparticles is affected by various parameters which include their size and their ability to inactivate cancer cells [3, 4]. In radiotherapy, ionizing radiations such as X-rays and gamma rays, high-energy particles are widely used for the treatment of cancer tumors in solid form. Unfortunately, ionizing radiations are not capable of detecting cancer cells from healthy cells [5, 6]. Therefore, healthy tissue is destroyed due to radiotherapy for eradicating cancerous cells.

The main purpose of using nanoparticles for specific tumors in radiotherapy is to improve the result of radiotherapy by increasing toxicity for tumors and reducing it for healthy cells [7, 8]. Among different nanoparticles, pre-clinical studies were done on gold nanoparticles for checking their sensitivity to radiation by different photon radiation [9, 10].

Among different nanoparticles, gold nanoparticles have unique features such as small size, good biological adaptability, and low toxicity. These features nominate gold nanoparticles to be used in various medical procedures like in biosensors, drug transition and in radiotherapy and chemotheraphy [11, 12]. Exposure dose stability and toxicity of gold nanoparticles were evaluated for radiotherapy purposes by Zhang and his colleagues. They did not observe any instability and changing in size in the spherical gold nanoparticles with diameter 15 nm, irradiated by gamma radiation with 2000 to 10000 roentgen. The toxicity results show that a high concentration of gold nanoparticles causes abnormal function of k 562 cells. This effect was not observed at low concentrations [13]. For photons with an energy of 500 kV, Compton scattering and excitation is observed. Compton scattering causes the excitation and generation
of Compton electrons. These electrons, in turn, cause the photoelectric effect. Rules of selection prevent photon emission after excitation.

Therefore, the emitted photon energy increases the temperature of the atomic network.

This process is known as the blackout process. At high energies that excite gold atoms, many photons are lost due to the photon-phonon transition process [11-13].

At energies higher than 1/02 mega electron volts, the pair production phenomenon occurs which results in the production of electron and positron pairs. In all the above interactions, except for Compton scattering, the cross-sectional area of stroke of the photon depends on atomic number (Z) in the photoelectric effect and Z2 and Z3 in the pair production phenomenon. Therefore, it is expected that in the interaction of X-rays and gamma rays with gold atoms, a considerable amount of energy will be transferred to gold nanoparticles in the form of free electrons and thermal energy [14-16].

2. Methodology

This study, conducted through a systematic review of Narrative Review, used key terms including Gold nanoparticles, radio sensitization, radiation therapy, cancer, and related factors through searching in databases. International scientific publications including PubMed, Web of Science, Google Scholar, Scopus, Elsevier and internal scientific databases including Barakat Knowledge System, Academic Jihad Scientific Database, MedLib, Magiran journals database, Civilica and a search on the WHO.

A total of 46 scientific sources including books, articles, theses, and reports published between 1989 and 2019 in English on the success of cardiopulmonary resuscitation and related factors were collected. Unrelated articles were excluded and references related to our review were studied. Finally, the number of articles and scientific sources were selected and analyzed according to the purpose of our study and according to the needs of the article.

3. Results

In a study by Cho and his colleagues, Using the Monte Carlo method, the effect of increasing dose from radiating of 140 kVp, 6MV and 4MV rays and gamma-ray source IR192 to gold nanoparticles were evaluated [17]. In another study by Cho, a feasibility study of applying the GNP as a facilitator in low energy radiotherapy was evaluated by using the Monte Carlo calculations [18]. In this study, X-ray with 50 kVp energy and brachytherapy sources I125 and Yb169 were used and the calculations of macroscopic dose enhancement factor (MDEF) were done with and without of GNP in the tumor. The dose increase reports more than 40% for the radiation sources used in this study in the presence of GNP. For a tumor with GNP and concentration of 18 mg Au/g that was mixed or loaded, 116%, 92%, and 108% MDEF were achieved respectively for I125, 50 kVp, Yb169 in 1 cm distance from the center of the source. While with a concentration of 7 mg Au/g, the above measurements became 68%, 57%, and 44% respectively for those sources. Based on the results, they conclude that GNRT can be performed clinically by using brachytherapy sources with low energy and high dose rate, like the Yb169 source.

From the code GEANT4 Monte Carlo, source IR192 was simulated and used as a standard for the validation of dosimetry data [19]. Two different types of geometry, including parallel radiation and 360 degree or 4π Ostradians are used to simulate Monte Carlo.

The parallel radiation is similar to radiating external radiation by using parallel radiation. The 100 nm gold nanoparticles were distributed equably in a 450 nm network region. In addition, the dose increase was stimulated by a mixture of water and gold nanoparticles with the same concentration.

For two parallel rays with 380 kV energy, the maximum dose increases were 28% and 36% for gold nanoparticles singly and water and gold nanoparticles mixtures, respectively. However, it should be noticed that the dose amounts for the photons passing through the region with the gold nanoparticles are lower than those without GNP. On the other hand, previous studies have shown an increase in the dose using GNP.

Also, the self-absorption phenomenon in a high atomic number region results in equable dose distribution in the treatment using GNP. According to Monte Carlo simulation, the highest dose increase with GNP is due to the photoelectric effect that is proportional to 1/E3. As we know, the edge energy of the k atom of gold is 80/7 keV.

In a study by Zhang and his colleagues, the effect of increasing dose for photons with energy up to 300 to 380 kV was investigated. The range of the photoelectrons produced in this study was about 85 µm, which is more than GNP size. Therefore, transmitting the energy of the photoelectrons around nanoparticles became more probable [7].

Cancer cells and tumors transplanted to tested mice with GNP in them were irradiated with a single dose of 25 Grays by using electron radiation with an energy of 2 MeV.

In addition, the amount of GNP accumulation in the cancer cells of the culture medium and mice was checked and measured. The results showed that the amount of GNP is statistically significant to the sensitivity of cancer nets to radiation in the culture medium (p value=0.02). This amount in mouse cancer cells is less than /05 (p value=0.05).

In addition, the programmed death rate in combined cells with GNP under irradiation is twice more than cells
without GNP. Chang and his teammates achieved more radio sensitization effect using GNP in size 13nm, in comparison with another study by Chithrani et al [20, 21].

In a pioneering study by Hainfeld, the toxicity of GNP was examined on cancer cells in mice [22]. Mice with breast cancer were divided into radio sensitization groups. The first group got GNP by injection equably before irradiated with a 250kVp radiation. The second group was only irradiated. The third group got GNP only 86% of the first group, 20% of the second group and none of the third group survived up to one year. Therefore, the presence of GNP in cancer cells results in increased tumor sensitivity to the radiation.

Zhang and his teammates studied the radio sensitivity of the GNP in prostate cancer [23]. DU-145 cells in the human prostate were exposed to X-ray with 200kVp energy in the presence of TGS-GNPs or Glucose-GNPs or GNPs singly. The results showed that TGS-GNPs or irradiating with X-ray induced inhibition of cancer cell growth by approximately 14% or 16% individually.

However, a combination of TGS–GNPs and X-ray produced inhibition of cell growth of 30.57%, while the combination of Glucose–GNPs plus X-ray induced inhibition of cell growth by 46%.

In an in vitro study by Kong and his teammates, two molecules including Cysteamine (AET) and thio-glucose (Glu) were synthesized with GNP, and its effect on the Radio sensitization of breast cancerous cells (MCF-7) against benign breast cells (MCF-10A) was studied. The results showed that more cancerous cells die in the presence of Glu-GNPs than GNP alone. The results show that the toxicity rate of GNP to the cells is very low. In this study different radiation such as 200 kVp X-ray and gamma-ray in radiotherapy were applied with and without GNP. The final results showed that in the radiotherapy with the presence of GNP, the death rate of cancer cells is significantly more than its rate without GNP [24].

Ngwa et al studied the radio sensitization effect of gold nanoparticles in size 50nm on Hela cells for low-energy brachytherapy sources and low dose rates [25]. In this study, source I-125 was used for exposing the Hela cells (with and without the presence of gold nanoparticles). The results showed that the biological effect on Hela cells when they are irradiated in the presence of gold nanoparticles with concentration 2 mg/ml is approximately 70% to 130% more when gold nanoparticles are not present. Also, in the non-irradiated state, the gold nanoparticles showed the least effect on the cancer cells.

Dosimetry is complex in the presence of nanoparticles and requires accurate tools to examine and measure the amount of energy changes in matter. Dosimetry gel is one of the most effective tools in this field. In this study, by using different concentrations of GNPs that placed in MAGIC-f gel, the increased dose is discussed, by dosimetry gel and Monte Carlo simulation under clinical X-ray irradiation [26-30].

In the study by Marques and his teammate, the possibility of dosimetry was evaluated by using MAGIC-f gel and in the presence of the gold nanoparticles. In this study, different concentrations of gold nanoparticles placed in MAGIC-f gel were exposed by 250 kVp X-ray. The results of this experiment were compared with the calculations performed by Monte Carlo simulation which showed more than 97% consistency at all concentrations between the simulated dose and the dosimetry gel. As the concentration of gold nanoparticles increases, the absorbed dose also increases [26].

Rahman increased, by using nPAG gel, increased absorbed dose rate in the presence of 2 nm gold nanoparticles and for radiation sources with energies of 80kV, 125keV, 6MeV and 6MV achieved 64%, 76%, 37% and 14% respectively [27]. The concentration of gold nanoparticles in this study was considered 1mM [27]. In studies by Khosravi et al, by using MAGIC-f gel and in the presence of 15 nm gold nanoparticles with concentration of 1 mm were performed for different modes of radiotherapy (external with energy 18MV, internal with source IR-192 and combinational), average values of absorbed dose measured by gel at the prostate zone within the pelvic phantom in the presence of gold nanoparticles in external, internal, and combined radiotherapy, respectively 9%, 15%, and 14% were more than the corresponding amounts in this organ, without gold nanoparticles [28-30]. The Monte Carlo simulation method also showed 8%, 14%, and 13% increase in dose for the same situation by using dosimetry gel.

In gamma test and in different modes of external, internal and combined radiotherapy, without the presence of gold nanoparticles, respective values including 92/6%, 86/4%, and 88/1 % were achieved, but in the same radiotherapy modes and in the presence of gold nanoparticles, the results of the test showed values of 94/7%, 91/7%, and 88/6 %, all of which are within acceptable range. Also, the comparison of the DVHs shows very good agreement between the results of experimental dosimetry (gel) and computational (Monte Carlo) [31, 32].

4. Discussion and Conclusions

The results of all studies in this field confirm the increase in dose forwarded to the tumor in radiation therapy using gold nanoparticles. The outcome of using GNPs for radiation therapy has been studied by several experimental investigations during the last years. Although the increase of radiation dose in tumors loaded with high-Z materials has been attempted for several decades, the emergence of new gold nanoparticles with biocompatible characteristics has attracted scientists to investigate their applications in conjunction with radiation...
therapy. There are controversial results about the impact of photon energy and GNP size in recently published articles. The results of the interaction of the energy of radiated photons with GNPs size is still a controversial issue. In other words, the Monte Carlo simulation uses gold nanoparticles in size about 10 to 100 nm, and in biological studies use these nanoparticles in size up to 1/9 nm. Finally, the most effective parameters that have been investigated and reported using the Monte Carlo simulation are larger nanoparticle dimensions, high molar concentration, and low-energy X-ray or gamma-ray photons that prepare a higher dose increase.

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