Evaluating the effect of Zinc Oxide nanoparticles doped with Gadolinium on dose enhancement factor by PRESAGE dosimeter

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ABSTRACT

Background: New treatment modalities are developed with the aim of escalating tumor absorbed dose and simultaneously sparing the normal structures. The use of nanotechnology in cancer treatment offers some possibilities including destroying cancer tumors with minimal damage to healthy tissues. Zinc Oxide nanoparticles (ZnO NPs) are wide band gap semiconductors and seem to have a good effect on increasing the absorbed dose of target volume especially when doped with a high Z element. The aim of this study was to evaluate the effect of ZnO NPs doped with Gadolinium (Gd) on dose enhancement factor by 6MV photon beam irradiation. **Materials and Methods:** Various concentrations of ZnO NPs doped with 5% Gd were incorporated into PRESAGE composition, the 3D chemical dosimeter. Then by using a UV-Vis spectrophotometer optical density changes and also dose enhancement factor (DEF) were determined. **Results:** The results of this study showed that by incorporating 500, 1000, 3000 and 4000 μg/ml ZnO NPs doped with Gd into PRESAGE structure the dose enhancement factor of about 1.57, 1.69, 1.78 and 1.82 in a 15 ×15 cm^2 field size could be found, respectively. **Conclusion:** The results of this study showed that ZnO NPs doped with Gd could be considered as new compound for increasing the absorbed dose.

Keywords: *Zinc Oxide, Gadolinium, Nanoparticle, PRESAGE, DEF.*

INTRODUCTION

Advanced treatment delivery techniques such as Three Dimensional Radiation Therapy (3DCRT), Intensity Modulated Radiation Therapy (IMRT), Stereotactic Radio Surgery (SRS), Stereotactic Radio Therapy (SRT) and Volumetric Modulated Arc Therapy (VMAT) are currently used with the ultimate goal of conforming the radiation dose in such a way that delivers maximum lethal dose to the target volume whilst minimizing doses to organs at risk [1,2]. These methods of treatment improve the therapeutic ratio and enable dose escalation in the target volume, hence reducing the radiation related complications and consequently cause the NTCP (normal tissue complication probability) and TCP (tumor control probability) curves to have a more disunion from each other [3,4].

The use of nanotechnology in cancer treatment offers some exciting possibilities including the opportunity of destroying tumors with lower doses and consequently lower

damage to healthy tissues [5-13]. There have been done several studies focusing on importance and influence of nanoparticles on increasing therapeutic ratio and also dose enhancement on irradiated volume especially by Gold nanoparticles [14, 15]. Among nanoscience, Zinc Oxide nanoparticles (ZnO NPs) are interesting wide band gap semiconductors (3.37 eV), capable of producing reactive oxygen species (ROS) and oxygen free radicals. ROS generation is linked to cell damage and cellular apoptosis [13, 16-18].

It is evident that high Z materials absorb X-ray significantly. Therefore, it is hypothesized that the interaction of ZnO NPs with X-rays could be optimized by the addition of rare earth (RE) elements as dopants. The probability of an X-ray photon being absorbed or scattered by a particular material is a function of photon interaction cross-section. A greatly enhanced photoelectric cross-section can be derived from the introduction of a material with a high atomic number (Z). If a high Z element could be readily and specifically incorporated into cells and then exposed to photons of energy just above the binding energy of the innermost orbital (K edge), a selective absorption might be induced. One such element that has precedent in medical diagnostics is Gadolinium (Gd) which has an X-ray photon interaction cross-section significantly greater than the elements that comprise biological tissues [19-21]. It seems that ZnO NPs doped with Gd have the potential to increase the total absorbed dose of irradiated volume and consequently not only lead to spare the surrounding normal tissues but also reduces the needed Monitor Unite (MU) to deliver that amount of dose. Protocols for these complex treatment delivery techniques have been developed to involve very steep dose gradients and are therefore, extremely sensitive to errors in treatment delivery. To minimize such errors, 3D dosimeters were developed as a relative method for improving dose monitoring and delivery [1,2].

One of the most significant developments in 3D dosimetry over the past decade was the introduction of radiochromic dosimeter (PRESAGE) [22-25]. PRESAGE dosimeter is not considered as a gel dosimeter, but rather a clear polyurethane resin containing radiation-sensitive reporter components (leuco dye) and halogenated carbon radical initiators. Free radicals result from the homolysis of the bond between carbon and the halogen upon irradiation. These radicals oxidize the leuco dye that is also incorporated in the formulation, leading to a change in color (optical density). The change in optical density is linear with respect to the absorbed radiation dose. According to previous studies, this type of dosimeter has the potential to be used in clinical dose measurements [22-25].

The aim of this study was to determine the dose enhancement factor of ZnO NPs doped with Gd as a novel nanoscale composition, by use of PRESAGE dosimeter, irradiating by 6MV photon beams.

MATERIALS AND METHODS

PRESAGE fabrication

At first, PRESAGE dosimeter was fabricated. The procedure of PRESAGE fabrication was as follows:

(i) Free radical initiator and reporter compound were thoroughly mixed. The chosen radical initiator and reporter compound were CCl_4 (Merck, Keinlworth, United States) and leucomalachite green (LMG) (Sigma Aldrich, St Louis, MO, United States), respectively. (ii) Polyurethane resin (Crystal Clear 2006, Smooth-On, Easton, PA, USA) was supplied in two parts (Part A and Part B). These compounds were mixed together to afford optically clear polyurethane resins that form the matrix of the PRESAGE dosimeter. (iii) The solutions prepared in steps (i) and (ii) were combined together and thoroughly mixed. (iv) The mixture prepared in step (iii) was poured into poly spectrophotometer cuvettes and the filled cuvettes were placed under certain pressure for a few days to minimize out gassing [22-25].

Polyurethane is approximately water equivalent but according to Mayneord formula, adding radical initiators and leuco dye cause the effective atomic number to be greater than that

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of water. Equation 1 shows Mayneord formula:

$$Z_{eff} = \sqrt[2.94]{f_1 \times (Z_1)^{2.94} + f_2 \times (Z_2)^{2.94} + f_3 \times (Z_3)^{2.94} + \ldots} \quad (1)$$

In which, f_n is the fraction of the total number of electrons associated with each element, and Z_n is the atomic number of each element [24].

In general, dosimetric properties of PRESAGE are affected by the fractional weight of its elements [22-26]. Therefore, the percents of components need to be arranged and calculated in such a way to be water equivalent.

In order to prepare an almost water equivalent dosimeter and also save other good dosimetric properties of PRESAGE including sensitivity, linearity, stability and etc. percentage of PRESAGE composition was adjusted according to the study done by Mostaar *et al.* [24].

By obtaining the chemical formulations of PRESAGE components and using Mayneord formula, the effective atomic number of fabricated dosimeter would be 7.8.

Read-out wavelength

At second step to determine the maximum absorption wavelength of PRESAGE, the absorption spectrum of PRESAGE filled cuvettes over the visible wavelength (470-750 nm) were obtained by use of a UV-Vis spectrophotometer (Varian, Palo Alto, California, USA). Then the maximum absorption of each cuvette was obtained pre irradiation.

Calibration

The next process was calibration of PRESAGE against ionization chamber (Farmer chamber, 0.6 cc, PTW, Freiburg, Germany) to deliver definite steps of absorbed dose. Cuvettes were placed in a solid water phantom made by Plexiglas (figure 1) and irradiated by 15×15cm² field to deliver the absorbed doses including 0, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 Gy irradiated by 6 MV photon beams producing by a linear accelerator (Varian Clinac 2100 C). Various slab phantoms were used to prepare the electronic equilibrium condition (figure 2) [27]. For each dose step, three cuvettes were used. All cuvettes were kept in dark and cold

environment to prevent any accidental absorption change and 48 hours after irradiation, the maximum absorption of each cuvette was obtained by using UV-Vis spectrophotometer, similar to pre irradiation phase. Finally, by subtracting the pre irradiation absorbance values from that of post irradiation, calibration curve which is the variations of optical density against absorbed dose, was plotted [28].

Nanoparticle synthesization

At the next section, ZnO NPs and 5% Gd doped NPs were prepared and incorporated in to the composition of the PRESAGE and the irradiation processes were repeated.

Nanoparticles were prepared by chemical precipitation route using Zinc acetate, sodium hydroxide, gadolinium nitrate and absolute ethanol.

Figure 1. A designed slab phantom .

Figure 2. Setup of calibration process.

Zinc acetate dehydrate (0.2195 g) was dissolved in 20 ml of absolute ethanol and stirred with a magnetic stirrer at room temperature, to be mixed thoroughly. Then the solution of NaOH (0.08g NaOH in 20 ml of absolute ethanol) was added dropwise into the solution of Zinc acetate under constant magnetic stirring for 1h. After that 0.015 mmol of oleic acid was added into the solution. The white powder was obtained after stirring this solution at room temperature for another 1 h. The prepared dispersion was centrifugally filtered and washed with ethanol and distilled water for several times, followed by drying in an oven at 50 °C for 4 h [29].

For doped ZnO nanoparticles the appropriate amount of gadolinium nitrate (5% w/w Zinc acetate dehydrate) was added in the homogenized and clear solution of Zinc acetate dehydrate and ethanol. The remaining procedures were the same as described above.

Incorporating NPs into PRESAGE

For determining the effects fabricated NPs on DEF, various concentrations of ZnO NPs and ZnO NPs doped with Gd were incorporated in to PRESAGE composition and irradiation and read out procedures were repeated.

Comparing the results

Finally, by applying descriptive statistics, the results of dosimetry at presence and lack of NPs were compared and dose enhancement factor was determined.
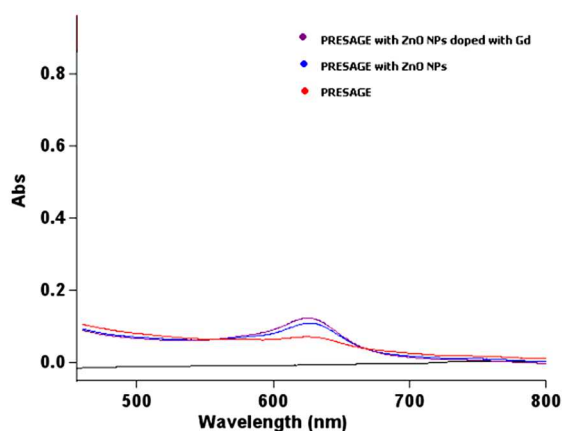
RESULTS

Read-out wavelength

Figure 3 depicts the absorption spectrum of different compositions of PRESAGE (with and without NPs) over visible wavelength. As it can be seen, the maximum absorption of all series of PRESAGE occurred at about 632 nm.

Calibration

Figure 4 represents the optical density changes of PRESAGE against various dose steps.

DEF determination

Dose enhancement factor (DEF) is defined as the ratio of changes in optical density with NPs over the optical density changes without NPs [14]. Since PRESAGE exhibits a linear behavior against various dose levels (figure 4), comparing the optical density changes of all series of PRESAGEs in a particular dose step is feasible.

Figure 5 shows the PRESAGE filled cuvettes with and without NPs, delivered a dose of 10 Gy. The color changes caused by presence of NPs are obvious.

Table 1 shows the optical density changes of all fabricated PRESAGEs irradiated by 6 MV photon beams and 10 Gy delivered radiation dose. According to definition of DEF, this parameter was acquired for different compositions of PRESAGE and tabulated in table 2. Comparisons of DEF for various concentrations of applied NPs are depicted in figure 6.
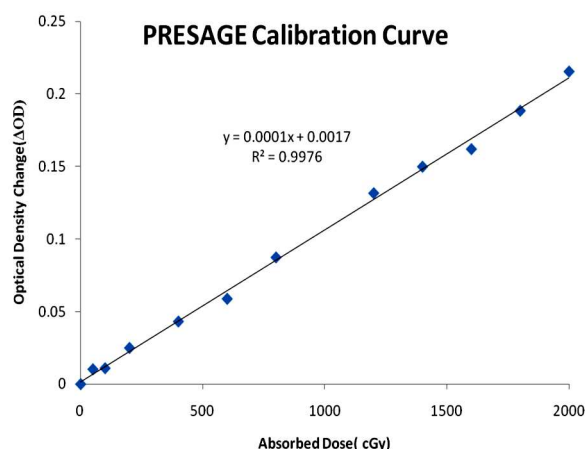

Figure 3. The absorption spectrum of various compositions of PRESAGE over visible wavelengths.

Figure 4. Calibration curve of PRESAGE.

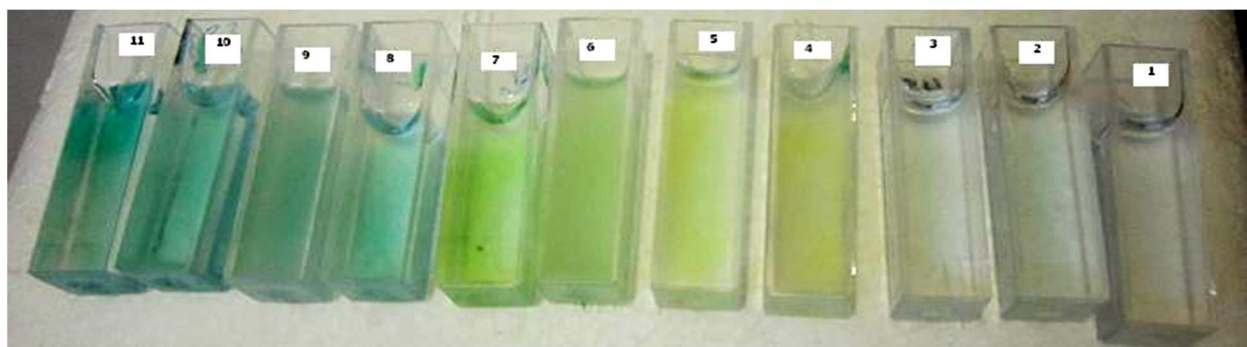*Int. J. Radiat. Res., Vol. 14 No. 2, April 2016*

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Figure 5. PRESAGE filled cuvettes with and without NPs at dose of 10Gy. 1) PRESAGE without NPs. 2) PRESAGE with 20µg/ml ZnO NPs. 3) PRESAGE with 20µg/ml ZnO NPs doped with %5 Gd. 4) PRESAGE with 500µg/ml ZnO NPs. 5) PRESAGE with 500µg/ml ZnO NPs doped with %5 Gd. 6) PRESAGE with 1000µg/ml ZnO NPs. 7) PRESAGE with 1000µg/ml ZnO NPs doped with %5 Gd. 8) PRESAGE with 3000µg/ml ZnO NPs. 9) PRESAGE with 3000µg/ml ZnO NPs doped with %5 Gd. 10) PRESAGE with 4000µg/ml ZnO NPs. 11) PRESAGE with 4000µg/ml ZnO NPs doped with %5 Gd.

Table1. Optical density changes of various PRESAGE compositions.

Concentration of NPs (µg/ml)	Added Composition	Optical Density Changes
-------	PRESAGE	0.1095
20	ZnO NPs doped with 5% Gd ZnO NPs	0.1099 0.1096
500	ZnO doped with %5 Gd ZnO NPs	0.1719 0.1445
1000	ZnO NPs doped with 5% Gd ZnO NPs	0.1850 0.1664
3000	ZnO doped with %5 Gd ZnO NPs	0.1945 0.1741
4000	ZnO NPs doped with 5% Gd ZnO NPs	0.1997 0.1807

Table 2. DEF of different compositions of PRESAGE.

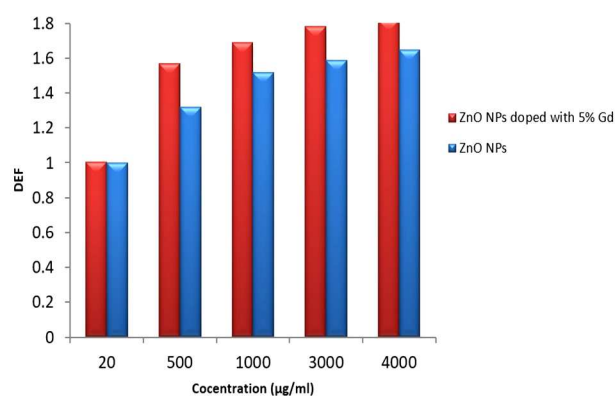| Concentration of NPs (µg/ml)	Added Composition	DEF
20	ZnO NPs doped with 5% Gd ZnO NPs	1.004 1.001
500	ZnO doped with %5 Gd ZnO NPs	1.57 1.32
1000	ZnO NPs doped with 5% Gd ZnO NPs	1.69 1.52
3000	ZnO doped with %5 Gd ZnO NPs	1.78 1.59

Figure 6. Comparisons of DEF for various concentrations of NPs.

DISCUSSION

High Z materials absorb X-ray significantly and Gd is a high Z element which can increase the probability of photoelectric effect when irradiated by photons [19, 20]. Although the probability of photoelectric effect for 6MV photon beams is low compared to orthovoltage beams, but regarding to the continues X-ray spectrum, attenuated photons, low energy photon beams in X-ray spectrum [30] and probably the pair production effect, DEF is clearly observed.

As it is shown in table 2 and figure 6, the maximum DEF is acquired by applying 4000µg/ml ZnO NPs doped with Gd. It is also shown that small concentration of NPs (20µg/ml) does not have a significant role in DEF even if it was doped by a high Z element such as Gd.

For delivering an absorbed dose of 10 Gy, an almost 995 MU was needed. Since by using 4000µg/ml ZnO NPs, for delivering the same absorbed dose, the needed MU would be below 600. This achievement can lead to decrease treatment time and therefore, treatment time reduction generally causes less patient movement during treatment and consequently random errors of treatment would dwindle which are the benefits of NPs application.

It is noteworthy to mention that Gd is a toxic element and toxicity is usually transferred from the surface of element [31]. Therefore, for increasing the absorbed dose it not feasible to use Gd without any surrounded structure. In other words, by doping the Gd into the Zinc Oxide NPs' crystal, Gd toxicity releasing to the neighboring atoms is omitted.

Type, size, concentration of nanoparticles and also the quality of photon beams are the items which have significant influence on DEF. Since there was not any study about the application of ZnO NPs with a high Z dopant as dose enhancing substance for megavoltage photon beams, it is not possible to make a comparison.

CONCLUSION

The results of this study revealed that ZnO NPs doped with Gd are new proposing substances for enhancing the absorbed dose and increasing the therapeutic ratio even in high energy photon beams. Various reasons may cause the DEF for 6MV photon beams such as photoelectric effect for low energy photon beams in continues X-ray spectrum, attenuated photons or pair production effect. Using these NPs not only reduces the needed MU to deliver a certain amount of absorbed dose, but also can lead to great succeeds in reducing treatment time and random errors in treatment procedure.

Conflict of interest: *Declared none.*

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