

Effect of Gold Nanoparticles on Dose Enhancement of 6 MV X-ray in MAGIC_f Polymer Gel Dosimeter

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ABSTRACT

Background: Currently, the potential application of gold nanoparticles (AuNPs) to increase the efficiency of radiation therapy has been widely investigated. However, lack of an appropriate method to estimate the dose distribution in a nanoparticle-laden tissue limits the applicability of nanoparticles in radiotherapy clinics. Polymer gel dosimetry provides an accurate and precise system that facilitates the measurement of dose distribution in full three dimensions.

Objective: In this study, the effect of radiation dose enhancement of AuNPs was assessed through gel dosimetry analysis.

Material and Methods: For this purpose, AuNPs were integrated in MAGIC_f polymer gel dosimeter and irradiated by 6 Mv X-ray beam. The irradiated gel was then evaluated through two modalities of magnetic resonance imaging (MRI) and optical computed tomography (OCT).

Result: MRI and OCT scanning of MAGIC_f gels containing 0.1 mM AuNPs demonstrated dose enhancements of 7.8% and 6.8%, respectively.

Conclusion: Polymer gel dosimetry has the potential to provide a new platform for the investigation and optimization of the applicability of nanoparticles in radiation therapy.

Keywords

Radiation Therapy, Gold Nanoparticles, Polymer Gel Dosimetry, Optical Computed Tomography

Introduction

Owing to its high atomic number (Z), gold nanoparticle (AuNP) enhances local absorbed dose of X-ray and may improve the efficiency of radiotherapy. Many studies have reported the promising role of AuNPs in the promotion of radiotherapy outcome. Hainfeld et al. first demonstrated the radio-sensitizing effect of AuNPs. They showed that the combination of AuNPs (1.9 nm) and 30 Gy radiotherapy dose (250 KVP) increased the one-year survival of the mice bearing mammary carcinoma from 20% for X-ray irradiation alone to 86% for the mice that were injected with 2.7 g Au/kg before irradiation.

Although positive impacts of AuNP on radiotherapy have been thoroughly accepted, the complexities relevant to the dosimetric evaluation of a nanoparticle-laden medium limit its applicability in clinical environments. Consequently, the primary mission of radiation dosimetry in

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the case of radio-monotherapy is to develop an accurate and precise system that facilitates the measurement of the dose distribution in nanoparticle-laden tissues.

Currently, water equivalent gel-dosimetry is proposed as a reliable three-dimensional (3D) dose verification system [1, 2]. Poly(acrylamide) gel dosimetry is a radiation-induced free-radical polymerization that occurs at the place of dose deposition. The 3D dose distribution pattern in gel dosimeters was initially imaged by magnetic resonance imaging (MRI) [3, 4]. In this case, quantitative MRI may be employed to measure one of the nuclear magnetic resonance relaxation times (normally T2), which can depend on the absorbed dose.

Although MRI has been effectively successful in measuring intricate dose distribution patterns and proposed as the gold standard read-out approach for gel dosimetry [5], there are significant drawbacks that might prevent its application to medical physics departments; the most important of these are the cost and availability of MRI scanners.

Currently, optical computed tomography (OCT) scanners have attracted increasing attention as a read-out approach for gel dosimetry that provides an easily available and low-cost bench-top scanner [6]. The idea of detecting dose distribution within polymer gels optically was first introduced in 1996 by Gore *et al.* [7]. OCT scanners exploit the fact that gel attenuates light, which changes as a function of the absorbed dose.

In the case of radio-monotherapy, gel dosimeters incorporated with AuNPs may provide a tissue equivalent medium that can suitably analyze the changes in dose painting due to nanoparticles presence in full three dimension. Marques *et al.* investigated the potential application of AuNPs in kilovoltage radiation therapy through gel dosimetry analysis. For this purpose, different concentrations of AuNPs were embedded in MAGIC_f gel dosimeter and irradiated with 250 KV X-ray (5 Gy).

Dose enhancement was quantified through comparing R2 signals (transverse nuclear magnetic resonance relaxation rate) acquired from MRI. Accordingly, MAGIC_f gels containing 0.02, 0.05 and 0.1 mM AuNPs present dose enhancement of 77%, 99% and 106%, respectively.

In this study, the radiation dose enhancement effect of AuNPs was assessed through gel dosimetry analysis. For this purpose, AuNPs were integrated in MAGIC_f polymer gel dosimeter and irradiated by 6 Mv X-ray beam. The irradiated gel was then evaluated by two modalities of MRI and OCT.

Materials and Methods

Nanoparticle Characterization

AuNPs were purchased from Nanobon Company (Tehran, Iran). The morphological investigation of nanoparticles was performed using Zeiss LEO 906 transmission electron microscope (TEM). The effective diameters of nanoparticles were measured through dynamic light scattering (DLS, Malvern Zetasizer Nano ZS-90).

Gel Preparation

MAGIC_f gel was prepared based on the formulation described by Fernandes *et al.* [8]. Briefly, the polymer gel dosimeter was manufactured on the bench top under a fume hood and normal atmospheric condition to achieve the highest reproducibility of gel preparation. To begin gel preparation, gelatin (Sigma-Aldrich) was added to deionized water at room temperature and then heated to 45°C, where the mixture was kept until gelatin completely melted. The heater was then turned off and the gelatin solution was cooled to 35°C, when ascorbic acid (Scharlou), formaldehyde (Merck) and copper sulfate (Merck) were added. After 5 min, the monomer (Methacrylic acid (Merck) was finally dissolved. Half of the solution was poured into cylindrical vials with a diameter of 1.2 cm and a volume of 8 mm³

which was considered as a control sample. AuNPs were immediately added to another half of the solution and were homogenized. The sample was poured into similar vials and labeled as Au-MAGIC_f gel. The amount of AuNPs dissolved in the solution was calculated to obtain the optimum concentration of 0.1 mM for megavoltage photons beam. Finally, samples were sealed with rubber caps and left to cool down at 10 °C for one day.

Gel Irradiation

Polymer gel dosimeters were irradiated approximately 24h post-manufacture with 6 MV photon beam of Siemens linear accelerator at Tehran Omid clinic. For background readings, three vials were kept un-irradiated. The geometry of gel irradiation is shown in Figure 1. The vials were located in a water phantom at the depth of 5 cm. The dose homogeneity was verified using a conventional treatment plan-

ning system. A square field (field size = 20 cm × 20 cm, source to the surface of phantom distance = 95 cm by SAD technique) was used for gel irradiation. The gels were irradiated with 0.5, 1.5, 2.5, 4 and 6 Gys.

Gel Imaging

MRI Scanning

To evaluate R2, MRI scanning was performed 2 days post irradiation using a 1.5 Tesla Siemens Vision scanner (Siemens, Erlangen, Germany) with a 16-echo multiple spins-echo pulse sequence. The samples were imaged according to the protocol summarized in Table 1.

To ensure that the obtained R2 values were not influenced by possible temperature gradients in the gel, gel vials were left in MRI room 4 hours before scanning. The vials were placed in the center of the head coil. R2 was calculated by fitting the image signal intensities to the following mono-exponential equa-

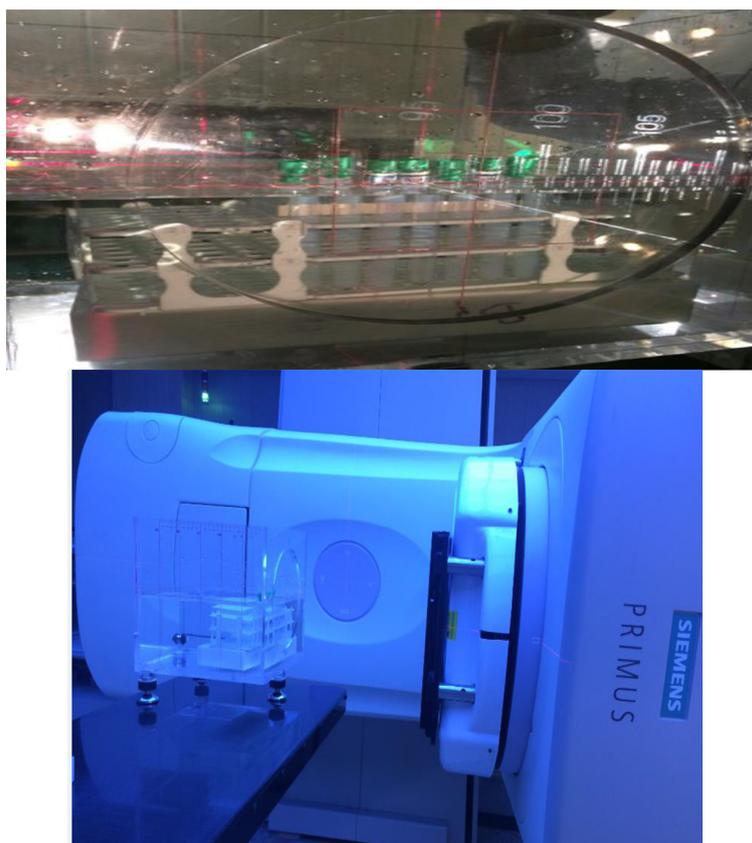


Figure 1: Irradiation set up of MAGIC_f gel dosimeter by linear accelerator.

Table 1: Imaging protocol of the polymer gels using 1.5 Tesla Siemens Vision scanner.

FOV	320mm
TE	22-352 ms
TR	3000 ms
Slice Thickness	3 mm
Matrix Size	320*320
Voxel Size	3*3*1 mm
NEX	3
Number of slices	5

FOV: Field of view; TE: Echo time; TR: Repetition time; NEX: Number of averages

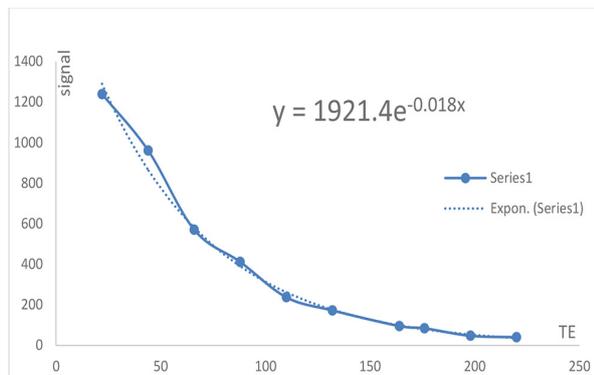
tion:

$$S_{SE}(TE) = S_{SE}(0) e^{-R2TE} + SLO(1)$$

where S_{LO} is the signal level offset and $S_{SE}(0)$ is the signal intensity at $TE = 0$ ms.

OCT Scanning

OCT scanning was carried out with a prototype direct-to-digital CCD (charged coupled device) video camera (14 bit- MINTRON-Germany, pixel numbers: 582*753 and SNR=58db) system, 2 days after irradiation too. Figure 2 shows a schematic view of the OCT scanner. For this purpose, gel vials were immersed in a rectangular water tank with clear side panels to avoid refractive effects at a vial-air interface, which would lead to reconstruction

**Figure 2:** Signal-TE curve of processed MRI data to obtain R2 for dose of 0.5 Gy ($R2=0.018$).

artifacts. Within the tank, the gel dosimeters were placed on a rotating turntable, centered on an angular guide. Step motor was attached to the turntable aided precise rotation of the dosimeter over the selected angular range that was 1.8 in our system, so 200 projections of any vials were acquired. The light source used emits most of its energy over a range of wavelengths about 560 nm (green light).

The CCD camera was placed on the opposite side of the tank from the light source and measured the amount of light attenuated by the water tank and gel vials in the beam.

Imaging was carried out in a darkened room to eliminate reflected light. Adjustable card board shutters were positioned between the diffuser panels and the water tank to collimate the light source to the width of the dosimeter array. This collimation was found to be useful in eliminating angle-dependent, tangential reflection of light from the surfaces of the outermost vials. The acquisition was carried out over a full 360° of rotation (200 projections by steps of 1.8 degrees).

The data received the central computer (PC) via a serial port. Data were collected and stored in a 2D matrix, then processed and filtered back projection using MATLAB software and reconstructed; transverse images could be depicted finally. In order to obtain a value representing the relative changes in image density as a function of radiation dose, circular regions of interest (ROIs) were drawn over each vial image, with care taken to avoid including the walls of the cylinders. Thus, the results reported here are given in terms of responses per vial per dose. Total grey-scale values or 'counts' from each ROI were copied to a spreadsheet program for analysis, and the dose-response curve was obtained for vials with and without AuNPs.

Result and Discussion

Figure 3 shows the TEM image of AuNPs, where dark regions correspond to nanoparticles. From the TEM image, it can

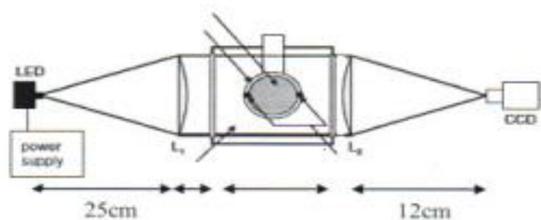


Figure 3: Shape of OCT used in this study.

be found that AuNPs are roughly spherical. Figure 4 shows the size distribution of AuNPs resulted from DLS analysis. Accordingly, the effective diameters of AuNPs were approximately 25 nm.

MAGIC-f response to the 6 MV X-ray beam was characterized by R2 signals relation to Dose. The calibration plots for MRI scanning of MAGIC-f with and without AuNPs are shown in Figures (5a) and (5b), respectively. The linearity of response to MAGIC-f was verified considering a dose range from 0 Gy to 6 Gy.

Figure 6 demonstrates the reconstructed transverse OCT images of the gels containing and not containing AuNPs irradiated with 0, 1.5 and 4 Gys. The reconstructed images were used to depict the OCT calibration curve as the change in optical attenuation versus dose (Figure 6).

As previously mentioned, AuNPs enhance the dose deposition in tissue equivalent gel. Table 2 indicates such dose enhancement quantified by comparing the R2 signals of MAGIC_f gels with and without nanoparticles in different doses. Accordingly, dose enhancement factor (DEF) due to the presence of AuNPs in MAGIC_f gels estimated by MRI is described as follows:

$$DEF = \frac{R2_{(Au-MAGIC_f)} - R2_{(MAGIC_f)}}{R2_{(MAGIC_f)}} \quad (2)$$

where, $R2_{(Au-MAGIC_f)}$ and $R2_{(MAGIC_f)}$ are the signals derived from MR images of MAGIC_f gel vials containing and not containing AuNPs, respectively. As a result, MRI scanning of the gel containing 0.1 mM AuNPs demonstrated

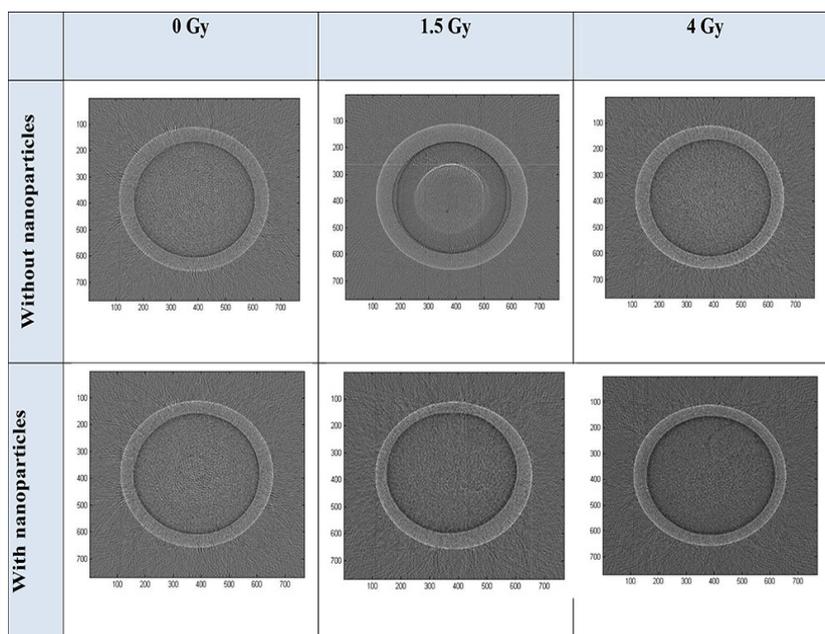
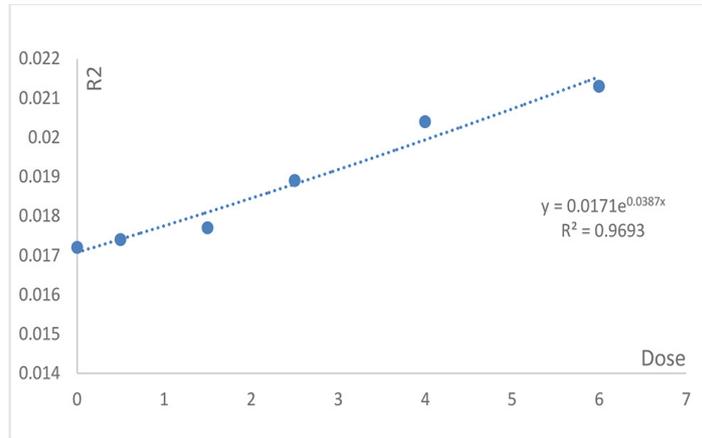
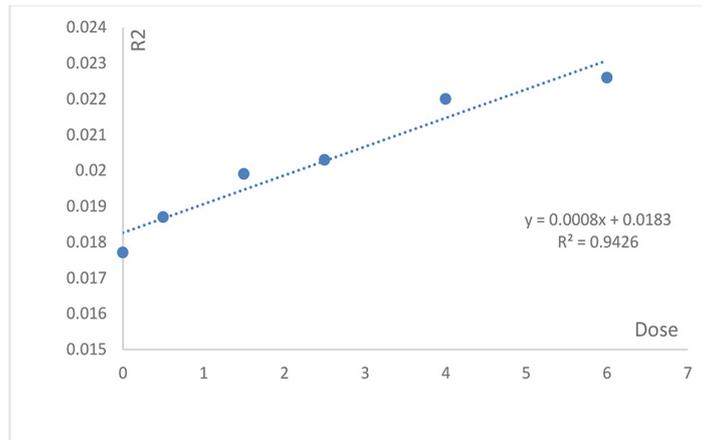


Figure 4: Reconstructed transverse images of polymer gels obtained from OCT.



(a)



(b)

Figure 5: Calibration curves of gel vials without(a) and with(b) AuNPs by processing of MRI image.

a DEF of 7.8% averaged from all different doses.

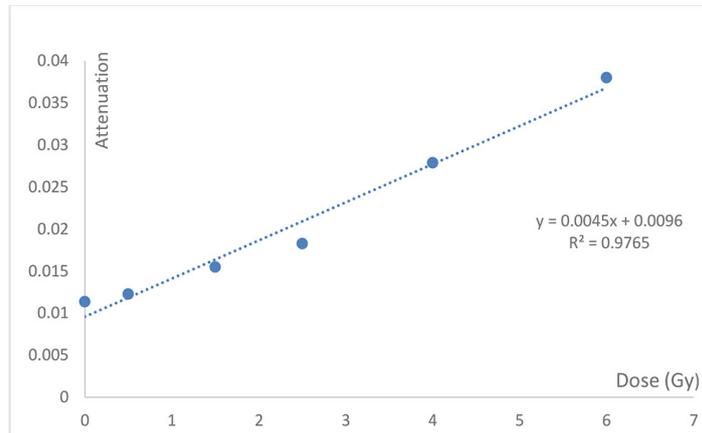
In the case of OCT imaging, irradiated gels containing AuNPs show higher optical attenuation as a comparison to the gels free nanoparticles at similar doses. Table 3 compares the optical attenuation of MAGIC_f gels with and without AuNPs in different doses. Accordingly, the dose enhancement due to AuNPs presence in MAGIC_f gel estimated by OCT can be calculated by the following equation:

$$\frac{\mu_{(Au-MAGIC_f)} - \mu_{(MAGIC_f)}}{\mu_{(MAGIC_f)}} \tag{3}$$

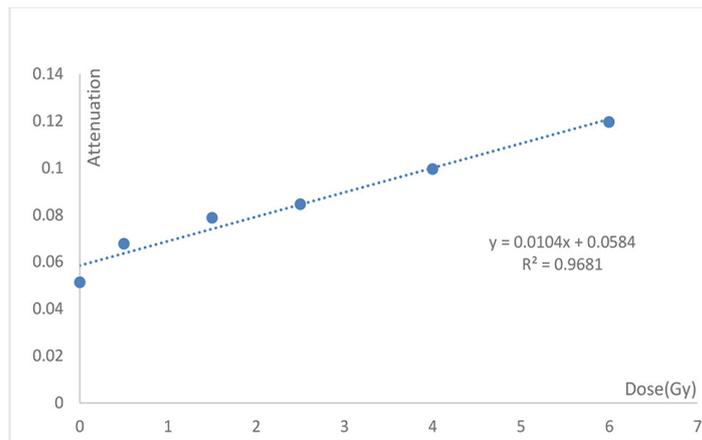
where, $\mu_{(Au-MAGIC_f)}$ and $\mu_{(MAGIC_f)}$ are the opti-

Table 2: R2 signals of MAGIC_f gels and resulting dose enhancement factor (DEF) due to presence of AuNPs.

Dose (Gy)	R2 (without AuNPs)	R2 (with AuNPs)	DEF
0	0.0172±	0.0173	0.6%
0.5	0.0174	0.0188	8.5%
1/5	0.0177	0.0192	8.4%
2/5	0.0191	0.0207	8.8%
4	0.0204	0.0223	8.2%
6	0.0213	0.023	8%



(a)



(b)

Figure 6: Signal-TE curve of processed MRI data to obtain R2 for dose of 0.5 Gy (R2= 0.018).

Table 3: Optical attenuation of MAGIC_f gels and resulting dose enhancement factor (DEF) due to presence of AuNPs.

Dose (Gy)	Optical attenuation (without AuNPs)	Optical attenuation (with AuNPs)	DEF
0	0.011363	0.01141	0.4%
0.5	0.012276	0.013173	7.3%
1.5	0.015482	0.0165658	7%
2.5	0.018257	0.019572	7.1%
4	0.027871	0.029933	7.3%
6	0.038	0.040698	7.1%

cal attenuations derived from OCT images of MAGIC_f gels containing and not containing AuNPs, respectively. The results of OCT scanning of the gel containing 0.1 mM AuNPs revealed a DEF of 6.8% averaged from all different doses. Therefore, OCT scanning underestimates the dose enhancement due to AuNPs presence in comparison to MRI scanning as the gold standard reading approach for gel dosimetry.

Conclusion

In this study, the radiation dose enhancement of AuNPs was verified by gel dosimetry analysis. Polymer gel dosimetry has the potential to provide a new platform for the investigation and optimization of the applicability of nanoparticles in radiation therapy.

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Conflict of Interest

Nothing to be declared.

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