RESEARCH ARTICLE

Gel dosimetry: The effect of gold nanoparticles on the dose enhancement in the external radiation therapy

Hossein Khosravi * [1], Bijan Hashemi [1] , Faezeh Rahmani [2]

[1] Department of Medical Physics, Tarbiat Modares University, Tehran, Iran

[2] Department of Physics, K. N. Toosi University of Technology, Tehran, Iran

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ABSTRACT

Background: Normoxic type MAGICA gel dosimeters are established for dose quantification in three dimensions for radiotherapy.

Objectives: The ability of MAGICA polymer gel was assessed by experimental measurements method for studying the effect of gold nanoparticles (GNPs) in dose enhancement under the external 18MV radiotherapy practices.

Methods: The different GNPs concentrations were studied: 0.02mM, 0.05 mM and 0.1 mM. Then, a new formulation of MAGICA gel was synthesized. The fabricated gel was poured in the tubes (with and without the GNPs) located at the water phantom. The water phantom was irradiated to 18 MV beam of a Varian linac. After 24 hours, the irradiated gels were read using a Siemens 1.5 Tesla MRI scanner. The absolute dose sat the reference points and isodose curves resulted from the experimental measurements of the gels following the external radiotherapy practices were compared.

Results: The signal of non-irradiated gel samples containing GNPs showed maximum difference of the 1% compared to gel without nanoparticles. The dose enhancement factors were 1.014±0.07, 1.074±0.11and 1.161±0.15 for 0.02, 0.05 and 0.1 mM concentrations, respectively. The results demonstrate that use of GNPs embedded in polymer gels caused the enhancement of radiation.

Conclusion: The results indicated that the polymer gel dosimetry method as developed and used in this study can be recommended as a reliable method for investigating the DEF of GNPs in external radiotherapy practices.

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INTRODUCTION

In recent years, the effect of gold nanoparticles (GNPs) in common radiotherapy has been studied extensively by using experimental measurements as well as Monte Carlo (MC) simulations. The idea of increasing the dose using some high-Z elements has been proposed several decades ago, but following the invention and compatibility of GNPs with biological systems, scientists have been encouraged to investigate further applications of such elements in radiotherapy. Gold atoms present in nanometer sized particles have their basic properties of metal type materials such as melting point, crystal structure, conductivity, magnetic properties and optical properties completely altered. Unlike their presence in bulk materials, their properties become more dependent on the size than chemical composition. This size dependent behavior is also

* Corresponding Author Email: *hossein.khosravi@modares.ac.ir*

known as quantum size effects. It occurs when the electronic structure of the metal changes from a continuum electronic band to discrete electronic levels. In bulk materials, there is no gap between the valence band and the conduction band whereas in nanoparticles this gap is present. The effect of this transition between quantum physics and solid state physics is what causes the size dependent quantization effects to occur. The results of the most studies in this field have confirmed the increase in the radiation absorbed doses of various tumors in the presence of GNPs. However, the results are still controversial regarding to the involved and prominent interaction processes of ionizing radiation with the GNPs which result Dose Enhancement Factor (DEF) in tumor. The most effective parameters such as the dimension of nanoparticles, high molar concentrations, and lower energies of the photons or gamma rays to obtain the higher doses have been investigated by experimental dosimetry as well as MC methods in various studies [1-14].

Polymer gel dosimeter is a promising type of radiation dosimetry method used in medical radiation therapy [15]. The advantages of gel dosimetry include tissue-like elemental composition, high spatial resolution, capability for three-dimensional (3D) dose measurements, and possibility of preparing dosimeters of varying sizes and geometries [16]. The tissue equivalent property of polymer gels also serves as a good phantom to simulate the application of medical radiation to the human body. Polymer gel dosimeters are able to measure the effects of contrasts agents or metallic radiation dose enhancers such as iodine and GNPs inside the dosimeter, directly. In gel dosimeters, contrast agents may have uniform dispersion within the dosimeter; therefore, the effects of this material can be directly quantified. Physical measurement of the dose enhancement produced by high Z materials with other types of radiation dosimeters, such as film and ionization chambers, are quite complicated, although there have been some attempts to use these dosimeters[17-18]. Physical measurement was done for dose enhancement produced by high Z materials such as iodine in normoxic polymer gels [19-21].

Measurements of the dose enhancement caused by high atomic number materials in polymer gels have been made using iodine [19–21]. These studies show that a contrast agent can be added to nPAG without changing the dose linearity properties of the gel. A linear relationship between spin and spin relaxation rates and delivered doses is conserved with addition of iodine. Fricke gels have been previously used to quantify the dose enhancement by gold microspheres [22]. However, Fricke gel failed to detect the expected dose enhancement when used to measure the dose enhancement of iodine [23].The MAGIC-f gel, as an appropriate three dimensional and tissue-equivalent dosimeter, has been successfully used to determine quantitatively the DEFs resulted from the presence of GNPs as a compatible radiosensitizer in various target organs. This gel can be used potentially to assess the effects of using GNPs in radiotherapy practices [24]. Recently, a normoxic polyacrylamide gel (nPAG) has also been used to measure the increase of the absorbed dose rate in the presence of GNPs at different energy ranges [25].

In this study, we developed a technique of measuring dose enhancement by using MAGICA doped with GNPs. Our measurement aims are determining the feasibility of using MAGICA+ GNPs as a dosimeter. We report the dose enhancement from megavoltage photon beam irradiation.

MATERIAL AND METHOD

GNPs preparation

In contemporary research, various synthesis techniques are being developed for GNPs fabrication. In this study, GNPs of 50 nm size were obtained from PNF Co. (Payamavaran Nano Fardanegar Co, Tehran, Iran) as GNPs in aqueous solution with 1mg/ ml (1000ppm) concentration. In PNF Company, nanoparticles are produced by applying extra high electric voltage and current and the primary bulk wire with 0.1mm diameter is then converted into the nanoparticles via pulse explosive process.

Gel fabrication

A MAGICA polymer gel dosimeter was prepared. All chemicals (gelatin, ascorbic acid, CuSO4.5H2O, hydroquinone and methacrylic acid) were provided by Sigma Aldrich with experimental grade. The preparation of the gel was carried out in a similar procedure as described by Fong et al. (2001) with slight difference due to the presence of agarose in MAGICA formulation [26]. Four samples were isolated from the same batch, in which three of them contained the GNPs. The sample not containing GNPs served as control.

Gel homogenization was achieved by routine mechanical mix without heating. Three different GNPs concentrations were considered: 0.02mM, 0.05mM and 0.1 mM (Molar amounts). Gel samples were not irradiated in the first 24 hours after being manufactured. All irradiations were performed after that period.

Megavoltage X-rays and electron beam irradiation

The gel samples were irradiated with 18 MV photon beams by using medical linear accelerator (Clinac 2100C, Varian Associates Inc). The gels were set up in water at SSD = 100 cm using a 25 × 25 cm^2 field size for photon beams) as shown in Fig. 1. Irradiations were also done in single fraction with constant dose rate of approximately 100 MU/min (equal to 1Gy/min in a reference phantom). The gel samples were placed in water and exposed to radiation reference doses of 0 to9Gy. The doses delivered by photon were verified with ionization chamber.

MRI scanning

Magnetic resonance images were acquired 1 day after irradiation using a 1.5T scanner (Seimens, Multi slice). This period was necessary to ensure that polymerization reaction was completed and thermal equilibrium between gel samples and MRI room temperature was reached. A fast-spin echo sequence has been used with following parameters: field of view = 300 × 300 mm^2, slice thickness = 4 mm, effective echo time TE = 22ms, repetition time (TR) = 3000ms, the matrix size = 256 × 256 matrix, pixel size= 1.2 ×1.2 mm^2, number of echo= 16.

Image and data processing

All of the image and data processing were done by using MATLAB software (version 7.4 math works). The measured dose maps were reconstructed from the R2 image. Each pixel value of the *R*2 image was obtained by fitting the T2 relaxation function to a plot of the pixel intensities in the base images versus the corresponding echo times on a pixel-by-pixel base. A dose map was obtained after correlating radiation dose to relaxation rate for each pixel of the *R*2 image.

The levels of the polymerization of the irradiated gels with and without GNPs were compared by calculating the R2 (1/T2). This shows the level of polymerization as a function to the dose. Fig. 2 showed the example of the T2 map from the MRI image.

Statistical analysis

This study presents results (mean values ± standard deviation) from 3 independent experiments. One way analysis of variance was used to determine the significance of the difference between the control and experimental group. A difference was considered to be statistically significant when $p<0.05$.

RESULTS AND DISCUSSION

Since the experiments were performed in water environment, the effect of contrast enhancement in MAGICA gel dosimeter with MRI technique was investigated to achieve good results. MR images in water and air were obtained while all other conditions of imaging were the same, e.g. in both

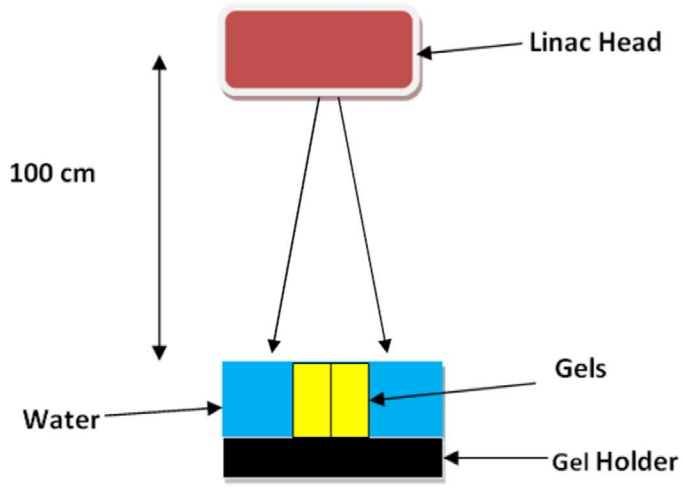

Fig. 1. The schematic illustration of the gel irradiation set up with 18 MV photon beams

cases containers fixed in the head coil and left for few minutes to avoid motion artifact due to water disturbance in the container.

MAGICA response to the 18 MV x-ray beam was characterized by R2 signal relation to dose (Fig. 2). A linear relationship was found between delivered dose and R2 for the MAGICA and MAGICA+ GNPs with 18 MV energy shown in Table 1. Fig. 3 shows calibration curve. For verification of dosimeter behavior of MAGICA polymer gel, ionization chamber dosimeter had been used. The experimental data are well fitted through a linear fit and good correlations are obtained for all of the experimental results. The effects of GNPs on polymerization of the unirradiated samples with and without GNPs were evaluated as shown Fig. 4. The lack of variation difference between MAGICA and MAGICA+ GNs which is less than 1 % indicates chemical interaction between GNPs and gels are negligible.

Table 1. The sensitivity and dose enhancement for MAGICA with and without 50 nm GNPs at different concentrations for 18 MV energy

Gel Type	Mean Sensitivity (10^{-3} s^{-1} Gy-1)	Mean DEF
MAGICA	6.3±0.20	
MAGICA+GNP(C=0.02 mM)	6.4±0.21	1.014±0.07
MAGICA	6.3±0.20	
MAGICA+GNP(C=0.05 mM)	7.3±0.32	1.074±0.11
MAGICA	6.3±0.20	
MAGICA+GNP(C=0.1 mM)	8.2±0.46	1.161±0.15

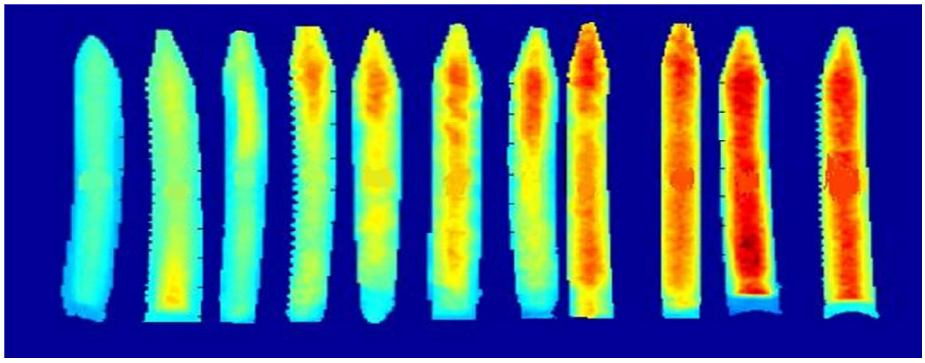

Fig. 2. The T2 map from MRI image of the gel samples

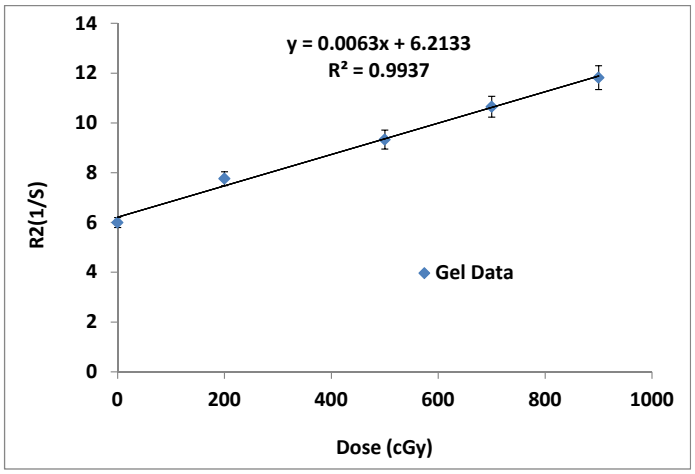

Fig. 3. MAGICA polymer gel dosimeter R2 response on absorbed dose in range of 0-900cGy

The dose–response slopes for R2 versus delivered X-ray dose for MAGICA+GNPs and pure MAGICA were calculated. The ratio of these slopes was taken as the dose enhancement factor (DEF) for the gel samples with and without GNPs (concentrations: 0.02, 0.05 and 0.1 mM). Concentration 0.1mM presents DEF of 1.161 in R2 related to gel without GNP; concentrations 0.05 mM and 0.02 mM present DEF of 1.074 and 1.014respectively (see Figs. 5-7).

Figs. 5-7 show dose enhancement effect caused by X-rays of megavoltage range of energies in gels with and without GNPs. Dose enhancement by high Z material is believed to be caused predominantly by enhancing the likelihood of the pair production interaction. When GNPs are added to the gel prior to irradiation and bombarded with megavoltage X-rays, the pair production interaction cross section will increase. This can be clearly inferred from the interaction probability of these X-ray photons with gold atoms compared to their interaction with the tissue equivalent medium such as water.

The outcome of this work demonstrates the feasibility of introducing GNPs into polymer gel dosimeters and the ability to scan them with the MRI scanner in the same way as standard polymer gel samples that do not contain metallic particles. The doping of polymer gels with metallic atoms such as iodine, gadolinium and recently GNPs have been demonstrated that the dose enhancement caused by the presence such metallic atoms can be separated from the dose deposited in the gels [20, 24]. Generally, dose enhancement is extracted from the comparison of the dose measured by gels with and without inclusion of the metallic atoms. The measured dose is related to the dose

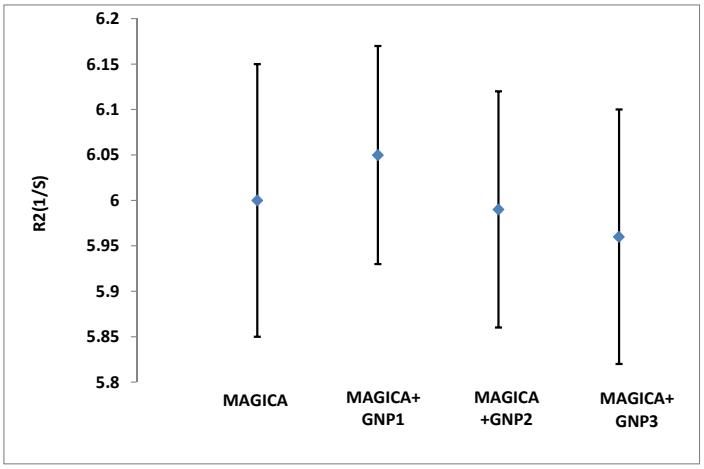

Fig. 4. Signal of non-irradiated gel samples with and without nanoparticles

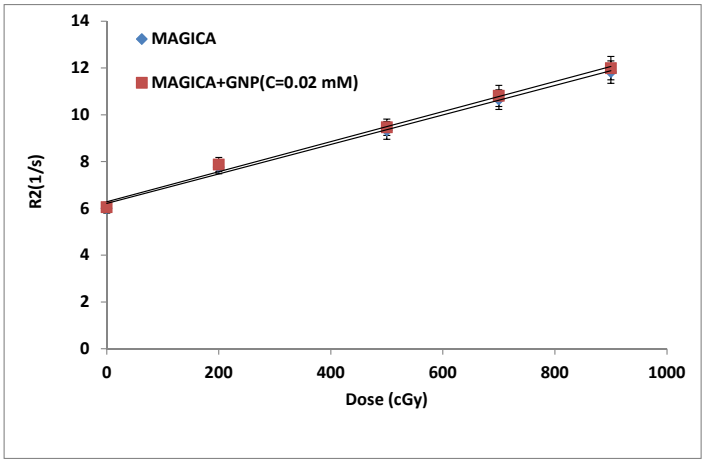

Fig. 5. Dose enhancement factor performed with MAGICA gel with 0.02 mM GNPs concentration

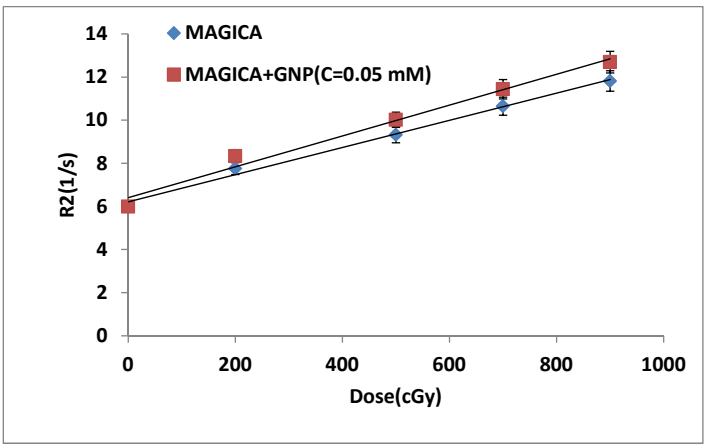

Fig. 6. Dose enhancement factor performed with MAGICA gel with 0.05 mM GNPs concentration

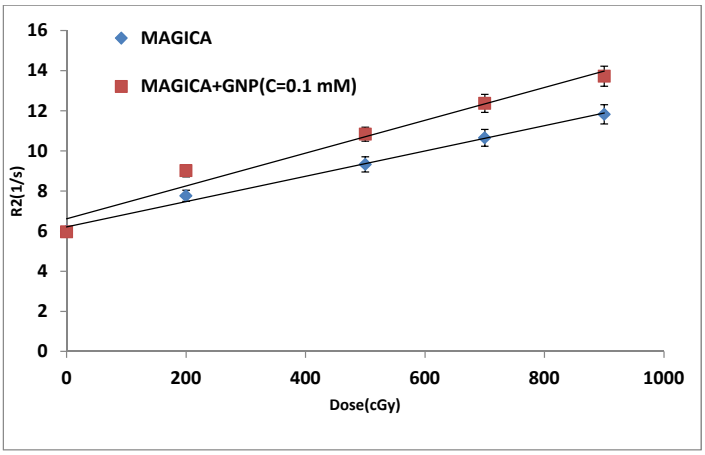

Fig. 7. Dose enhancement factor performed with MAGICA gel with 0.1 mM GNPs concentration

indicator factor "T2" of the MRI parameter for the two gels. However, inclusion of contrast agent or nanoparticles into polymer gel must take into account its chemical properties that will eventually affect the measured dose. Iodinated compounds have been observed to interfere with the interaction processes between the ions and monomers [27].

CONCLUSION

We reported here the measurement of radiation dose enhancement generated by GNPs using polymer gel dosimeters as a phantom. This study found a significant dose enhancement from the inclusion of the GNPs within polymer gels irradiated with megavoltage X-rays beams from a clinical LINAC.

One of the polymer gels advantages is the ability to measure the effects of contrasts agents or metallic radiation dose enhancers such as iodine and GNPs inside the dosimeter directly. In the gel dosimeters, contrast agents may have uniform dispersion within the dosimeter and therefore the effects of this material can be directly quantified. Physical measurement of the dose enhancement produced by high Z materials with other types of radiation dosimeters, such as film and ionization chambers, are quite complicated According to the experimental and simulation results, by adding of GNPs to the MAGICA polymer gel absorbed dose is increased. This study evidences polymer gel dosimetry as a suitable tool to perform dosimetric investigations of nanoparticles applications in Radiation Therapy.

Recently it has been shown that this high dose injures the normal tissue and induces the death of half of the animal samples indicating the need for

delivery of such a technique at much lower doses which can be done by inclusion of the GNPs in the target prior to irradiation [28]. We are hoping to extend this work by focusing on the application of GNPs as a dose enhancer for external radiotherapy. Polymer gels will be one of the useful tools to measure the dose enhancement by GNPs in addition to in vitro and in vivo study.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

REFERENCES

1. Hainfeld JF, Slatkin DN, Smilowitz HM. The useof gold nanoparticles to enhanceradiotherapy in mice. *Phys. Med. Biol.,* 2004; 49(18):N309-15.
2. Cho SH. Estimation of tumor dose enhancement due to gold nanoparticles during typical radiation treatments: a preliminary Monte Carlo study. *Phys. Med. Biol.,* 2005; 50(15):N163–73.
3. Chithrani BD, Ghazani AA, Chan WC. Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells. *Nano. Lett.* 2006; 6(4):662–8.
4. McMahon SJ, Mendenhall MH, Jain S,Currell F. Radiotherapy in the presence of contrast agents: a general figure of merit and its application to gold nanoparticles. *Phys. Med. Biol.,* 2008; 53(2):5635-51.
5. Zhang SX, Gao J, Buchholz TA, Wang Z, Salehpour MR, Drezek RA. Quantifying tumor-selective radiation dose enhancements using gold nanoparticles: a montecarlo simulation study. *Biomed. Microdevices.,*2009; 11(4):925–33.
6. Zhang XD, Guo ML, Wu HY, Sun YM, Ding YQ, Feng X, Zhang LA. Irradiation stability and cytotoxicity of gold nanoparticles for radiotherapy. *Int. J. Nanomed.,* 2009; 4:165–73.
7. Cho SH, Jones BL, Krishnan S. The dosimetric feasibility of gold nanoparticle-aided radiation therapy (GNRT) via brachytherapy using low-energy gamma-/X-ray sources. *Phys. Med. Biol.,* 2009; 54(16):4889–905.
8. Heuvel FV,Locquet JP, Nuyts S. Beam Energy Considerations for Gold Nano-Particle Enhanced Radiation Treatment. *Phys. Med. Biol.,*2010; 55(16):4509-45015.
9. Jain S,Coulter JA, Hounsell AR, Butterworth KT, McMahon SJ, Hyland WB. Cell-Specific Radiosensitization by Gold Nanoparticles at Megavoltage Radiation Energies. *Int. J. Radiat. Oncol. Biol. Phys.,* 2011; 79(2): 531–539.
10. Coulter JA, Jain S, Butterworth KT, Taggart LE, Dickson GR, McMahon SJ. Cell type-dependent uptake, localization, and cytotoxicity of 1.9 nm gold nanoparticles. *Int. J. Nanomed.,* 2012; 7: 2673–2685.
11. Ngwa W, Korideck H, Kassis AI, Kumar R, Sridhar S, Makrigiorgos GM. In vitro radiosensitization by gold nanoparticles during continuous low-dose-rate gamma irradiation with I-125 brachytherapy seeds. *Nanomed: Nanotech. Bio. Med.,* 2013; 9(1): 25–27.
12. Berbeco RI, Korideck H, Kumar R, Sridhar S, Detappe A, Ngwa W, Makrigiorgos M. Targeted Gold Nanoparticles as Vascular Disrupting Agents During Radiation Therapy. *Int. J. Radiat.Oncol. Bio. Phys.,*2014; 90(1): S198.
13. Wolfea T, Chatterjeea D, Leea J, Granta JD, Bhattaraia S, Tailora R, Goodrich G,Nicolucci P, Krishnan S. Targeted gold nanoparticles enhance sensitization of prostate tumors to megavoltage radiation therapy in vivo. *Nanomedicine: Nanotech. Bio. Med.*,2015;11(5):1277-83.
14. Rengan AK, Bukhari AB, Pradhan A, Malhotra R, Banerjee R, Srivastava R, et al. In Vivo Analysis of Biodegradable Liposome Gold Nanoparticles as Efficient Agents for Photothermal Therapy of Cancer. *Nano. Lett.,* 2015; 15 (2): 842–848.
15. De Deene Y, Hurley C, Venning A, Vergote K, Mather M, Healy B J and Beldock C.A basic study of some normoxic polymer gel dosimeters. *Phys. Med. Biol.,* 2002; 47: 3441–3463.
16. Gustavsson H, Back SJ, Medin J, Grusell E, Olsson L. Linear energy transfer dependence of a normoxic dosimeter investigated using proton beam absorbed dose measurements. *Phys. Med. Biol.,*2004; 49(17):3847-3855.
17. Robar JL, Riccio SA, Martin MA. Tumour dose enhancement using modified megavoltage photon beams and contrast media. *Phys. Med. Biol.,*2002; 47: 2433-2449.
18. Morris KN, Weil MD, Malzbender R. Radiochromic film dosimetry of contrastenhancedradiotherapy (CERT). *Phys. Med. Biol.,* 2006; 51: 5915-5925.
19. Boudou C, Troprès I, Estève F, Elleaume H. Preliminary study of a normoxic poly acrylamide gel doped with iodine. *J. Phys. C. S.,*2006; 56(1): 145-148.
20. Boudou C, Tropres I, Rousseau J, Lamalle L, Adam JF,Estève F, Elleaume H.Polymer gel dosimetry for synchrotron stereotactic radiotherapy and iodine dose enhancement measurement. *Phys. Med. Biol.,* 2007; 52: 4881-4892.
21. Gastaldo J, Boudou C, Lamalle L, Troprès I, Corde S, Sollier A, Rucka G, Elleaume H. Normoxic polyacrylamide gel doped with iodine: Response versus Xray energy. *Eur. J. Radiol.*, 2008; 68(3):S118-20.
22. Herold DM, Das IJ, Stobbe CC, Iyer RV, Chapman JD. Gold microsphere: a selective technique for producing biologically effective dose enhancement. *Int. J. Radiat. Biol,.* 2000; 76(10):1357–1364.
23. Corde S, Adam JF, Biston MC, Joubert A, Charvet AM, Esteve F, Le Bas JF, Elleaume H, Balosso J. Sensitivity variation

of doped Fricke gel irradiated with monochromatic synchrotron X-rays between 33.5 and 80 keV. *Radiat. Prot. Dosimetry.,* 2005;117(4):425-31.

24. Marques T, Schwarcke M, Garrido C, Zucolot V, Baffa1 O , Nicolucci P. Gel dosimetry analysis of gold nanoparticle application in kilovoltage radiation therapy. *J. Phys. C. S.* 2010; 250(1):012084.
25. Rahman W N, Christopher J, Wong C J. Polymer gels impregnated with gold nanoparticles implemented for measurements of radiation dose enhancement in synchrotron and conventional radiotherapy type beams. *Australas. Phys. Eng. Sci. Med.,* 2012; 35(3): 301-9.
26. Fong PM, Keil DC, Does MD, Gore JC. Polymer gels for magnetic resonance imaging of radiation dose distributions at normal room atmosphere. *Phys. Med. Biol.,* 2001;46: 3105-3113.
27. De Deene Y, Van de Walle R, Achten E, De Wagter C. Mathematical analysis and experimental investigation of noise in quantitative magnetic resonance imaging applied in polymer gel dosimetry. *Signal Process.,*1998; 70(2):85-101.
28. Meesat R, Jay-Gerin JP, Khalil A, Lepage M. Evaluation of the dose enhancement of iodinated compounds by polyacrylamide gel dosimetry. *Phys. Med. Biol.,* 2009; 54(19):5909–5917.