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ORIGINAL PAPER

Investigation of the dose enhancement factor of high intensity low mono-energetic X-ray radiation with labeled tissues by gold nanoparticles

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Abstract. The aim of radiotherapy is to maximize the dose applied to the tumor while keeping the dose to the surrounding healthy tissue as low as possible. To further enhance dose to a tumor, techniques to radiosensitization of the tumor, using high atomic number elements, have been proposed. The aim of this study was to investigate the influence of using gold nanoparticles as a contrast agent on tumor dose enhancement when the tissue is irradiated by a typical mono energy X-ray beam. To improve the conventional radiotherapy enhancement of the absorbed dose in a tumor tissue and to spare the skin and normal tissues during irradiation in the presence of concentration agent, a model based on a Monte Carlo N-Particle eXtended (MCNPX) computer code has been designed to simulate the depth dose in a phantom containing an assumed tumor. Test was carried out in two phases. In phase 1, verification of this model using the MCNPX was evaluated by comparing the obtained results with those of the published reports. In phase 2, gold was introduced into assumed tumor inside the phantom at different depths in the simulation program. Simulation was performed for four different concentrations of gold nanoparticles using a low mono-energetic parallel beam of synchrotron radiation. The obtained results show that the optimum energy for dose enhancement is found to be around 83–90 keV for all gold concentrations. The dose enhancement factor is increased linearly with concentration and diminished in depth along the central beam in the tumor. This approach of introducing contrast agents in conventional radiotherapy could hopefully prepare new treatment planning and improve the efficiency of tumor therapy.

Key words: radiation therapy • energy optimization • dose enhancement factor • dose absorption • gold nanoparticles • MCNPX code

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Introduction

Delivering a lethal dose of radiation to a tumor while sparing nearby normal tissues remains the greatest challenge in radiation therapy. To fulfill this goal, treatment methods are applied which deliver highly localized dose distributions. Localized dose distributions provide a maximum dose to the lesion, while simultaneously minimizing the dose to normal tissues. Several treatment techniques have been devised to produce highly localized dose distributions. Examples of these treatments include: boron neutron capture therapy (BNCT), stereotactic radio surgery (SRS), microbeam radiation therapy (MRT) and intensity modulated radiation therapy (IMRT) [1, 5, 17, 26].

To further enhance the dose to the tumor, techniques to radiosensitization of the tumor, using high atomic number elements, have been proposed in the past [12, 15, 18, 21, 23, 24].

Iodinated contrast agents, which are routinely used to improve contrast in X-ray diagnostic radiography, have been successfully proven to enhance radiation effects in kilovoltage X-ray radiotherapy beams [2, 4, 15, 23, 24]. The use of other high atomic number (Z) materials such as gold nanoparticles may also have

advantages in terms of radiation dose enhancement. The dose delivered to a tumor during photon-based radiation therapy can be enhanced by loading high atomic number (Z) materials such as gold (Au, Z = 79) into the tumor, resulting in greater photoelectric absorption within the tumor than in the surrounding tissues. At kilovoltage energy, the high photoelectric cross-sections of high atomic number materials result in substantial photoelectric interactions. The high linear energy transfer (≈ 11.5 keV·μm^{-1}) and short range of the photoelectric interaction products (photoelectrons, characteristic X-rays and Auger electrons) produce a localized dose enhancement. Experimental evidence has demonstrated dose enhancement *in vitro* and in solid tumors [3, 8, 10, 14]. Dose enhancement up to more than a factor of 100 was found in the environment of tissue-equivalent polymethylmethacrylate (PMMA) close to the surface of a thin metallic gold foil for heavily filtered X-rays (40 to 120 kV tube potential) [19]. They showed the secondary electrons with a range up to some 10 μm in tissue-equivalent material.

The use of gold nanoparticles as a dose enhancer seems more promising, than the earlier attempts using microspheres and other materials, for two primary reasons. First, gold has a higher Z number than iodine (I, Z = 53) or gadolinium (Gd, Z = 64), while showing little toxicity, up to at least 3% by weight, on either the rodent or human tumor cells [10]. Because the atomic photoelectric cross-section is approximately proportional to $Z^4 \sim Z^{4.6}$, the photoelectric interaction probability associated with a gold-loaded tumor, for example, is higher by at least a factor of 2 than that associated with a gadolinium-loaded tumor, assuming the same concentration of materials in the tumor and the same radiation quality. Thus, gold clearly leads to a higher tumor dose than either iodine or gadolinium. Secondly, nanoparticles provide a better mechanism than microspheres, in terms of delivering high-Z materials to the tumor, overcoming some of the difficulties found during an earlier attempt using gold microspheres [10].

Also gold is relatively passive and can be biocompatible. Nanoparticles clear the blood less rapidly than small molecules, such as iodine contrast media that are considered extravascular and exit the vascular system rapidly. Nanoparticles can stay in the blood for hours if designed to do so, thus enhancing tumor delivery. Effective tumor targeting with antibodies, peptides or drugs may be possible with nanoparticles. Target sites on tumor cells are limited and one or a few iodine atoms per antibody does not deliver enough high-Z material; conversely one antibody attached to one 15 nm gold nanoparticle would deliver 70 000 gold atoms. Gold nanoparticles have a number of surface ligands, allowing flexible design and multi-functionality by incorporating mixed ligands for optimal properties. The biodistribution of gold can be imaged before a therapeutic dose is delivered and used for treatment planning and quantified prediction of dose enhancement [7].

The low efficiency of X-ray kilovoltage machine in the absorbed dose in a tumor on the one hand, and unwanted absorption of low energy photon by skin on the other hand make it less practical in actual clinical application. Elimination of low energy photons causes more reduction of particle flux. Synchrotron application, however, is more advantageous regarding the above limitations. This allows a higher intensity photon with a small energy band and lower geometric penumbra due to almost parallel beam generation and, therefore, a lower level of photon scattering in the tissues. Since the pieces of work done by other authors in general, include more usage of X-ray kilovoltage machine. Our attempt was to investigate the problem using mono-energetic synchrotron radiations to activate nanogold particles of different concentration at different depth when introduced into an assumed tumor phantom.

Material and methods

MCNPX [22] is a general purpose Monte Carlo code which permits the description of the transport of different particles in arbitrary materials. Photons, electrons and neutrons, as well as other 29 particles between leptons, baryons, mesons and even light ions can be considered. The upper energy limits for electrons and photons are 1 and 100 GeV, respectively. A lower limit of 1 keV is fixed for these particles. The angular deflections in the multiple scattering of electrons are calculated according to the Goudsmit and Saunderson theory [6]. When electron energies are below 0.256 MeV, the corresponding cross-sections are obtained from numerical tabulations developed by Riley *et al*. [20]. For higher energy electrons, the cross-sections are approximated as a combination of the Mott and Rutherford cross-sections [16], including a correction factor which takes care of the screening. The particle tracking is governed by EMCPF which is the upper energy limit for detailed photon physics treatment (MeV), EMAX which fixes the upper limit for electron energy (MeV) and the lower energy cut-offs. In our simulations we have used the version 2.4.0 [9].

The Monte Carlo technique is valuable for this study because it allows investigation of dose enhancement produced by a wide range of photon energy and with a broad range of gold concentrations.

According to the energy of primary and secondary photons in this work, our simulations include photoelectric effect, Compton scattering and Rayleigh scattering. Compton scattering and photoelectric effect are the most important phenomena in this study. The elastic scattering, ionization and Bremsstrahlung effects were considered for the electrons produced from photon interactions with matter. Here, the Bremsstrahlung effect is negligible as its probability decreases for low-energy electrons and low atomic numbers of the medium [13]. The elastic scattering of electrons is of particular importance since it contributes to the dose of areas not directly exposed to irradiation.

The current investigation was conducted with several phantom test cases that simulated typical radiation treatments using several X-ray beams (60–115 keV). In each case, it was assumed that the gold nanoparticles were uniformly distributed throughout the tumor. The geometry used for the external beam cases simulated a tumor infused with contrast agents (iodine or gold nanoparticles) within a tissue phantom (16 × 16 × 16 cm^3). The size of the tumor was 2.2 × 2.2 × 2.2 cm^3. The center of the tumor was located along the central axis of the beam.

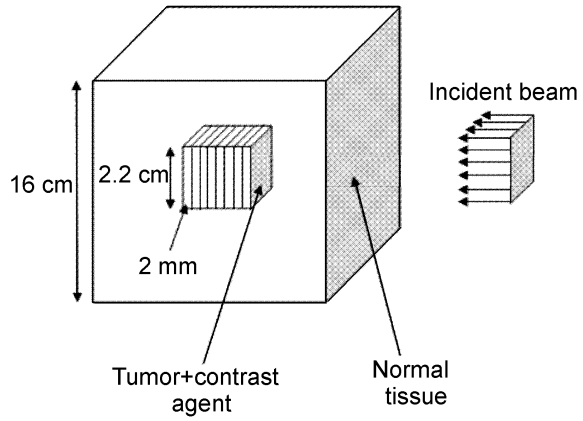

Fig. 1. Geometry for Monte Carlo calculations.

The field size of normally incident X-ray beams were defined at a source-to-surface distance of 50 cm, and was 2.2 × 2.2 cm^2 (Fig. 1).

In the first step in order to verify our simulated models, a tumor with iodine concentration at 4 cm depth in phantom was simulated and the results of dose enhancement were compared with the reported results [25]. In the second step the beam energy for maximum dose enhancement was investigated for a tumor located at 3 cm depth inside the simulated phantom. This energy was used for a concentration of 10 mg/ml gold nanoparticles introduced to a tumor at a depth of 3, 5 and 7 cm inside the phantom then dose enhancement factors were compared.

The material composition of the tumor and phantom taken was the same as the 4 component tissue (i.e., 10.1% hydrogen, 11.1% carbon, 2.6% nitrogen and 76.2% oxygen) with a mass density of 1 g/cm^3, defined by the International Commission on Radiation Units and Measurements [11].

The tumor was activated, using four different concentrations of 10, 25, 50 and 75 mg/ml composition and density of the tumor were altered by given levels of gold nanoparticles concentrations as listed in Table 1.

The phantom and tumor were subdivided into scoring voxels (slab) sufficiently small with a thickness of 2 mm to record the variation of dose in depth along the axis of the beam.

To assess radiation quality effects of the presence of the high-Z constituent in the contrast medium, Monte Carlo calculations of dose distribution in the phantom were performed.

A total of 107 primary particles were simulated in each run. All unidirectional photons were assumed to impinge perpendicularly on the cubic phantom and tumor surface to resemble a monoenergetic polarized synchrotron radiation. In all cases, the relative error of the absorbed dose was less than 2%.

The results of this simulation reveal a dose increase in a cancerous tissue in respect to surrounding healthy tissue. This approach improves the efficiency of the conventional radiotherapy technique.

Results and discussion

Verification of the Monte Carlo model

The dose enhancement factors (DEF), defined as the ratio of the average dose in the tumor region (or slab) with gold nanoparticles to that with no gold nanoparticles. The dose enhancement factor for different level of photon energy and the concentration of 50 mg/ml of iodine in a tumor at a depth of 4 cm in a phantom was compared with the work done by Verhaegen *et al.* [25] under similar condition. The results confirm our simulated model as shown in Fig. 2. From this section, we conclude that the simulated model is valid. In the remainder of the study we will investigate further effective factors in this method.

Table 1. Composition by weight fractions for a tumor labeled with contrast agent used in this study

Contrast-agent concentration (mg Au·ml^{-1})	Mass density (g·cm^{-3})	Weight fraction of atomic constituent				
		H	C	N	O	Au
10	1.01	.10	.11	.026	.754	.01
25	1.025	.098	.108	.025	.743	.024
50	1.05	.096	.106	.025	.726	.047
75	1.075	.094	.103	.024	.709	.07

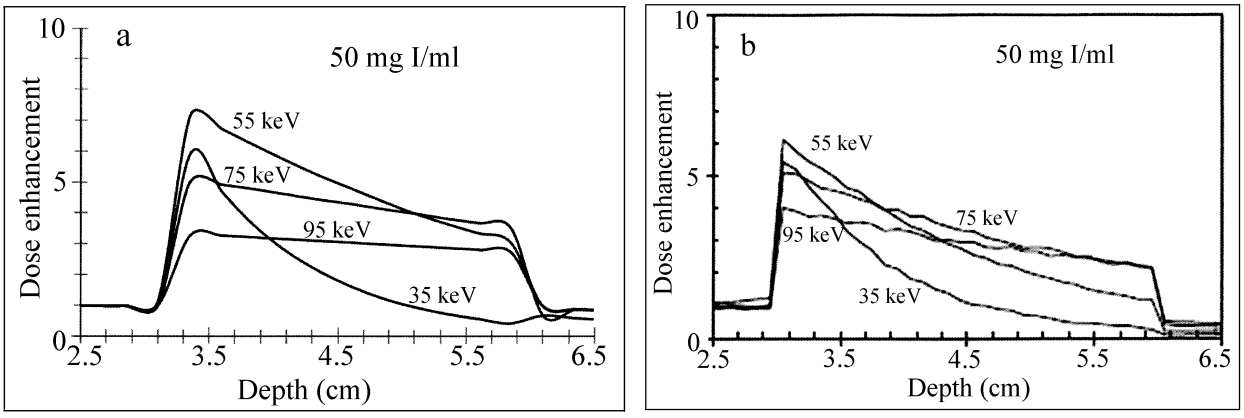

Fig. 2. Dose enhancement due to various proton energy and concentration of 50 mg/ml of iodine: a – this work; b – from Verhaegen *et al.* [25].

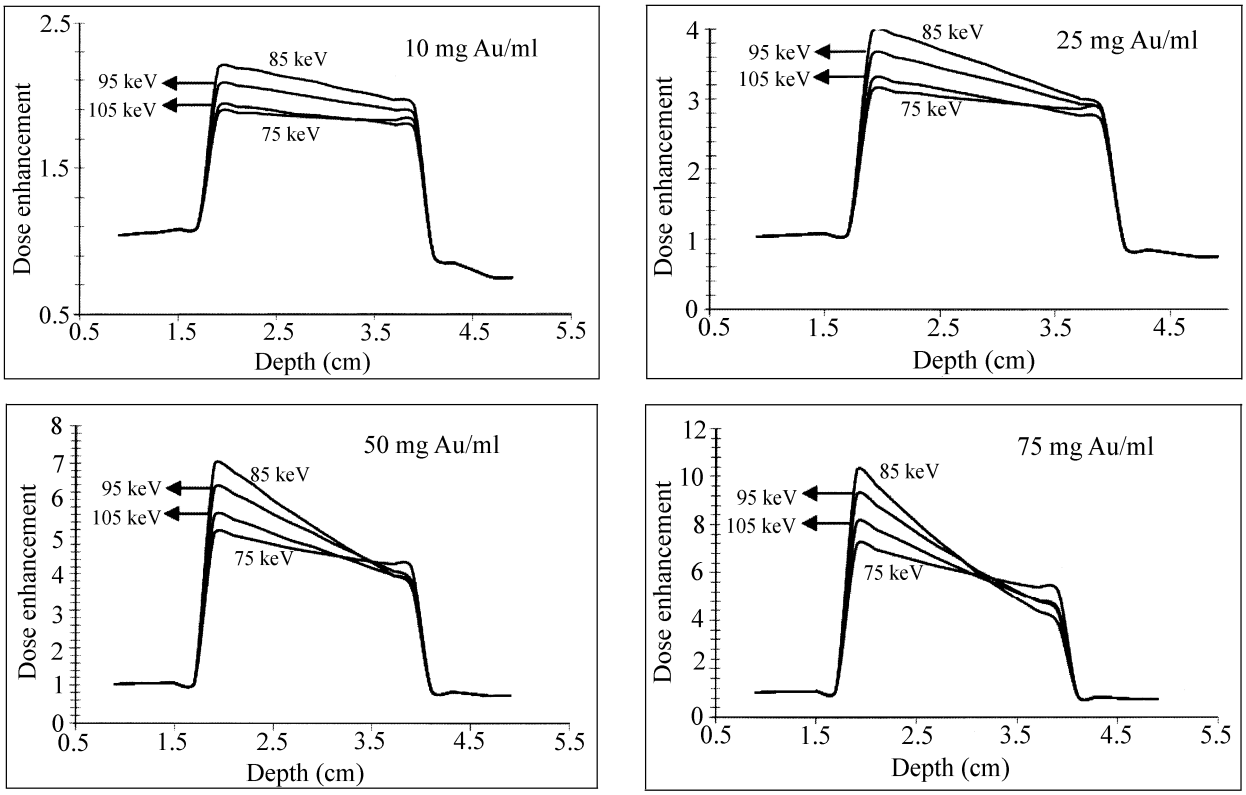

Fig. 3. Dose enhancement in a slab region extending from 2 to 4.2 cm for different beam of mono-energetic photons impinging on the phantom for various concentrations of gold contrast agent.

Effect of various concentrations on dose enhancement

Figure 3 shows that the dose is always enhanced significantly in the contrast-agent-enriched region for any photon energy in the range of 75–105 keV, but the largest dose enhancements are achieved for photon energy levels exceeding the *K*-edge (the *K*-edge for gold is 80.7 keV). This rise is due to the higher energy absorption coefficients in the contrast region and lower absorption in the normal tissue region. The enhancement dose is higher in the beginning of the tumor because of more photons having energy capable to induce photoelectric interaction with heavy particles.

The largest dose enhancements are obtained for the higher concentrations of contrast agent. The percentage of dose enhancement at the interface of normal tissue and tumoral region increases with increase of agent concentration. For certain photon energy, the homogeneity of DEF vs. depth in the tumor reduces as the concentration of contrast agent increases. This steep dose gradient can be explained by the increase of self-absorption happening within the contrast region at the begging of the tumor, where the intensity of the photons is rather high.

The degrees of reduction in dose uniformity along the central beam axis for different concentrations of gold nanoparticles are compared with the amount of reduction for a concentration of 10 mg/ml of gold. This reduction is a factor of about 3.5, 6 and 9 for concentration of 25, 50 and 75 mg/ml, respectively. For higher increase in gold concentration (if possible) besides imposed toxicity on cell tissues, the slope of DEF vs. depth diagrams becomes greater for higher concentrations. Based on the extent of the agent concentration in order to establish dose uniformity along the tumor, factors such as beam quality, multi directional sources and the angles in-between with possible filter wedges should be investigated.

Figure 4 gives DEF as a function of tumor gold concentration for two different energy levels (85 and 115 keV).

The dose enhancement factor increases almost linearly with increase in gold agent concentration with regression of 0.9996 and 0.9984 for 85 and 115 keV, respectively. The linearity aspect is in good agreement with the result obtained by Solberg *et al.* [24] for iodine concentration. Using different field size in a Monte Carlo calculation, Solberg *et al.* showed that the dose enhancement factor varies linearly with iodine concentration in a tumor.

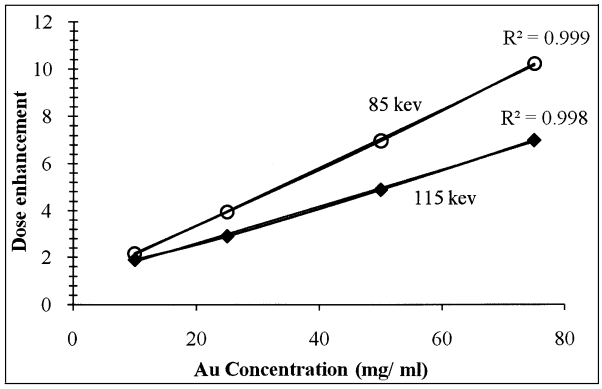

Fig. 4. DEF vs. gold concentrations for 85 and 115 keV beam energy.

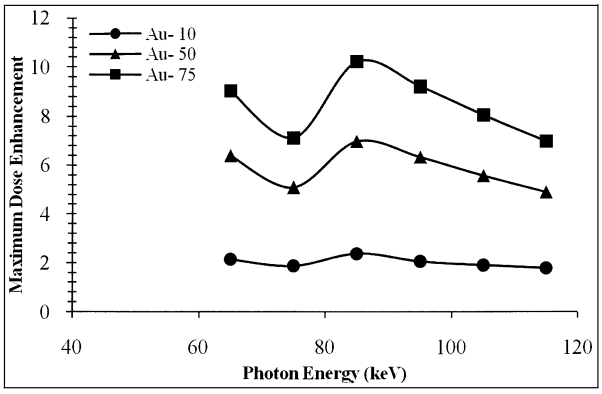

Fig. 5. Dose enhancement factor vs. photon energy for three different gold concentrations.

Effect of source energy on dose enhancement

Figure 5 shows the dose enhancement factor as a function of energy for three different gold concentrations in 10 keV energy intervals.

The total attenuation cross-sections of gold and soft tissue show that gold is significantly a better absorbent, especially around certain energies. The attenuation for gold just above the *K*-edge threshold at 80.7 keV is estimated at 8.9 cm^2/g in comparison to 0.184 cm^2/g for tissue at this energy. The absorbed dose enhancement at observed range of energy is explained by not only the increased interaction cross-section as higher *Z* for gold, but production of subsequent cascade of Auger electrons energy cannot be ignored. Some of these electrons can have ranges in tissue that are smaller than the cell radius and may contribute more to dose enhancement.

The optimum energy for maximum enhancement of dose in the tumor region was found to be about 82–87 keV.

The range of optimum energy is found to be the same for all concentrations. The higher gold concentration by theory causes more photoelectric interaction and so a greater increase in dose enhancement.

Effect of depth on tumor dose

Figure 6 shows the relative dose at different depths in the tumor for 85 keV photon energy. The optimum energy was used for irradiation of phantom with 10 mg/ml of contrast agent in the tumor and the relative depth dose for different position of tumor in the phantom was calculated. The results show as the tumor depth increases, the relative dose will decrease. It reaches near the skin dose at about 7 cm depth. All doses are normalized to skin dose.

To deliver a given dose to higher depths in the phantom, it may exceed the threshold of skin dose and violate the skin sparing. To limit this overestimation of skin dose, the aid of multi-directional beam and a careful treatment plan should be employed.

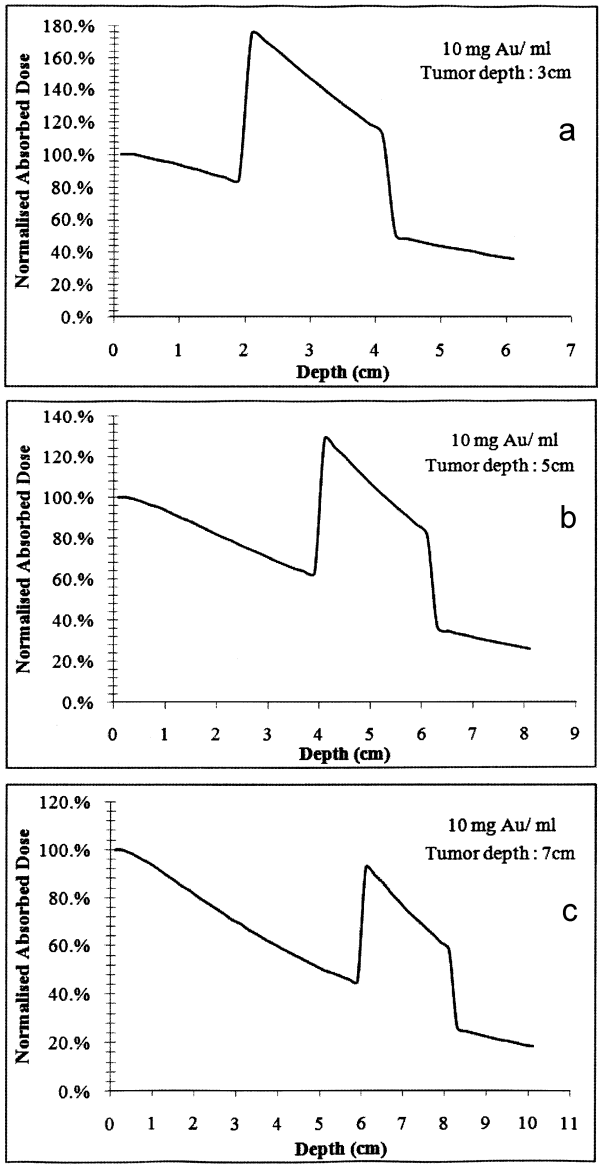

Fig. 6. Tumor dose due to irradiation by optimum energy using 10 mg/ml gold concentration: a – at 3 cm depth; b – at 5 cm depth; c – at 7 cm depth.

Conclusion

In this work, the dosimetric characteristics of high intensity low mono-energy X-ray radiation interacting with labeled tissues by Au nanoparticles were investigated. The dose enhancement in regions labeled with contrast agent (gold) was studied as a function of photon energy and contrast-agent concentration.

The obtained results show that the dose enhancement is more noticeable in the labeled gold nanoparticles. Maximum dose enhancements were found to occur for photon energy of around 82–87 keV.

The percentage of dose enhancement at the interface of normal tissue and tumoral region with 10, 25, 50 and 75 mg/ml of gold nanoparticles was found to be about 120, 400, 700 and 1040, respectively. The results show that for mono-directional irradiation of tumor in the presence of gold particles, the uniformity in dose along the tumor becomes severed as a result of increase in agent concentration by a factor of about 3.5, 6 and 9 in reference to 10 mg/ml concentration, respectively. Although it is possible, in principle, to obtain results for higher concentrations of gold, it has not been clinically tested for concentration above 20 mg/ml in animals.

This might be due to possible toxicity of gold for concentrations above 30 mg/ml.

In this study, the advantage of using synchrotron radiation over a kilovoltage beam is on the one hand the high intensity of low energy photons, and on the other hand the polarization of synchrotron beam that the later causes smaller scattering outside the beam path that would lower the delivery of dose to normal tissues. To lower even more and concentrate the energy more into the tumor, by collimation of synchrotron beam using slit collimators used in MRT can be a suggestive technique. It seems that the normal tissues not directly irradiated is adequately preserved, resulting in a rapid regeneration of blood vessels in the directly irradiated areas of normal tissues. This approach of using high intensity low mono--energy beam of synchrotron radiation and collimating into a microbeam along with the use of multi-directional source using a careful selection of plan parameters can suggest a new treatment planning and may improve the efficacy of tumor therapy application.

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