Calculation of radiation dose enhancement by gadolinium compounds for radiation therapy

G.A. Abdullaeva, G.A. Kulabdullaev, A.A. Kim; A.F. Nebesny, D.O. Yuldashev
Institute of Nuclear Physics, Academy of Sciences of Uzbekistan, Tashkent

Corresponding author: kulabdgairat@mail.ru

Abstract. In this study, we evaluate the features of dose enhancement with Gd contrast agent (Magnevist). Due to the increased relaxation time and high atomic number (z=64) Gd can be used in radiation therapy as a radiosensitizer. To perform a quantitative evaluation of the radiosensitization effect is determined a parameter called the dose enhancement factor - DEF. The DEF values were calculated based on the analysis of the mass absorption coefficients for gadolinium and biological tissue. An increase in DEF is observed when the radiation energy is higher than the K-shell ionization energy of Gd atoms. For the presence of 20315 ppm Gd contrast agent in biological tissue the dose enrichment factor is maximum DEF = 4.12 at photon irradiation energy 60 keV. Also, based on calculations for photon irradiation sources considered high degrees of dose enhancement occur for Am-241, Yb-196, and 100 kVp X-ray tube.

1. Introduction
Radiotherapy is the delivery of a high therapeutic dose of ionizing radiation within the tumor volume without exceeding the tolerance of surrounding healthy tissues. The use of radiotherapy at the doses necessary to destroy certain tumors then has limited by unacceptable damage to surrounding healthy tissues. The administration of high atomic number (Z) elements within the targeted tumor volume is the potential to make the cells more sensitive to radiotherapy using low-energy photon radiation (of the order of 100 keV). Indeed, materials containing high atomic number elements have different absorption properties from those of the surrounding tissues. Their presence can modify the absorbed dose distribution: it is thus possible to increase the local dose in regions where the radiosensitizing agent is located, without affecting healthy tissues [1].

Previous studies have taken advantage of the preferential uptake of certain contrast agents by tumors to increase the therapeutic ratio (delivered dose/tolerance of surrounding healthy tissues) by modifying the interaction cross sections of the lower energy photons near the tumor area, thus delivering a high, localized dose to the tumor. When the concentration of contrast agents is maximum within the tumor volume to be treated and minimum at the level of healthy tissues, the target volume can then be irradiated by X-rays. Contrast agents based on high atomic number elements such as iodine (Z = 53) have a high probability of low-energy photon interaction (~ 100 keV) by the photoelectric effect. The high linear energy transfer (LET) and a short range of photoelectric interaction products (photoelectrons, characteristic X-rays, Auger electrons) produce an increase in the dose localized in the tumor. It is therefore possible to observe an increase in damage at the level of tumor cells close to the radiosensitizing agent [2, 3]. Also, because of its biocompatibility in vitro and
in vivo, metallic gold (Z = 79) has been used. For about twenty years, it has been the subject of much research as a radiosensitizing agent. Several radiosensitization tests have been conducted with gold nanoparticles as a radiosensitizing agent. The strong photoelectric absorption and secondary electrons caused by X-rays or $\gamma$ can accelerate DNA strand breaks, demonstrating a clear improvement in radiotherapy through the shadowed use of gold nanoparticles and X-rays [4-6, 2]. The potential of translating preclinical studies on metal-based nanoparticles-enhanced radiation therapy into clinical practice is also discussed [7] using examples of several metal-based NanoEnhancers (such as gold-based nanoparticles CYT-6091, gadolinium-based nanoparticles AGuIX, and hafnium-based nanoparticles NBTXR3). In [8] study, gadolinium oxide nanocrystals (GONs) were synthesized using a polylol method to decipher the radiosensitizing mechanisms in non-small cell lung cancer (NSCLC) cell lines irradiated by carbon ions. In [9] review, are summarized the applications of radiosensitizers, including small molecules, macromolecules, and nanomaterials, especially those that have been used in clinical trials. The result still cannot meet clinical translation needs.

Limiting the dose of irradiation delivered to healthy tissues is a major concern in all radiotherapy procedures. The combined use of a radiosensitizing agent and X-rays destroys the same fraction of cells as during conventional radiotherapy (X-rays alone) with the difference that the irradiation doses are reduced. Therefore, if the same local control can be obtained for external irradiation doses of an order of magnitude lower, healthy tissue are less exposed to radiation.

This work aim is to evaluate dose enhancement with an MRI contrast agent - Magnevist containing Gd for the method associated with an original concept in cancer radiotherapy: to increase the lethal efficiency of low-energy X-rays, thanks to a targeted photoelectric interaction, by X-ray tube radiation, on a pharmacological agent located in the close vicinity of tumor cells or within them.

2. Accumulation more energy in tissues loaded with contrast agents

The photoelectric effect, inducing an attenuation of the primary radiation, contributes to the movement of secondary electrons in the medium. The medium (biological tissue) absorbs the kinetic energy of the electrons, thanks to the ionization and excitations they cause the dose reflects this amount of energy absorbed. Between the absorbed dose and the mass coefficient of energy absorption exists the direct relationship. At equal energy fluencies, it seems logical to think that the absorbed dose in a material will be higher if it is composed of elements of high atomic numbers: the sharp increase in the coefficient of total attenuation of photon radiation must necessarily result in this increase. But what then becomes of the optimal irradiation energy? Is a photon energy is located just above the threshold K still interesting to deposit a maximum of energy despite a kinetic energy of the photoelectron K practically zero? What quantities of heavy elements are necessary in biological tissues to obtain a significant gain in absorbed dose?

In the first approximation consider the mass coefficient of energy absorption and discontinuities. It is appropriate to take as reference biological tissue and to study as a function of the irradiation energy the possible dose gain by adding elements of high atomic number to it. As an example the relative variations in the total mass attenuation - $\mu/\rho$, and the mass energy-absorption - $\mu_{\text{en}}/\rho$ coefficients for pure gadolinium and biological tissue are shown below (Fig. 1).
Figure 1. Comparison of total mass attenuation and mass energy-absorption coefficients for gadolinium (blue and green) and biological tissue (red and black). [10].

In the first approach, we note that the discontinuity K of gadolinium, which was relatively large in the case of the total attenuation coefficient (14.83 cm$^{-2}$/g), seems a priori less interesting from the viewpoint of energy-absorption (2.39 cm$^{-2}$/g). The photoabsorption in gadolinium medium during the passage of the absorption threshold K consequently resulted in the formation of fluorescence photons or braking radiation. In comparison, these secondary photonic radiations have influence around the thresholds L (Table 1).

| Gd (cm$^{-2}$/g) | K shell      | L$_1$ shell    | L$_{II}$ shell | L$_{III}$ shell |
|-----------------|--------------|----------------|----------------|-----------------|
|                 | 50.239 keV   | 8.376 keV      | 7.930 keV      | 7.243 keV       |
| $\mu/\rho$      | 18.640       | 3.812          | 419.0          | 363.1           | 414.9          | 304.9          | 384.4          | 142.9           |
| $\mu_{en}/\rho$ | 5.585        | 3.199          | 370.2          | 322.3           | 366.5          | 275.5          | 345.2          | 137.9           |

If the energy located beyond the absorption threshold K therefore does not seem a priori optimal to deposit a maximum of energy in the tissues loaded with heavy elements, is now a question of which energy would be more suitable for this purpose. Using biological tissue as a reference and assuming that the irradiation energy fluencies are identical for the pure element and biological tissue, we studied the possible dose gain as a function of the irradiation energy if the interaction occurs on elements of high atomic number [11]. Except for elements whose atomic number is close to 70, the energy located just beyond the threshold K is therefore not optimal for increasing energy deposition compared to water equivalent tissues. This optimum is located at energies above the threshold K, for elements whose atomic number is less than or equal to 70 such as Br (42 keV), Ag (47 keV), I (48 keV), Sm (60 keV), Gd (60 keV), Yb (64 keV). It is lower than the excitation energy of the threshold K and higher than that of the thresholds L for heavier elements such as Pt (38 keV), Au (40 keV), Bi (40 keV) [11-12].

Some elements are more suitable than others to maximize the absorption of energy with respect to water equivalent tissues. It is interesting that for an energy range centered on the optimum and wide by about ten keV the energy deposition increase factor does not fall beyond 5% of the value of the
maximum. The absolute values of these maxima will not be discussed here since it is illusory to imagine being able to incorporate into humans pure elements as a substitute for water equivalent tissues. It therefore seems more reasonable to discuss the effect of dilutions of heavy elements in biological tissue. Since in this study we discuss the Gd contrast agent Magnevist. Our interest in the radiosensitizing properties of gadolinium is because we previously conducted studies of the pharmacokinetics of Magnevist with intratumoral and intramuscular administration in animals and on the accumulation of gadolinium in glioma tumors of the human brain [13-15]. Thus, in our experiments on small animals with intratumoral administration, the concentration of Gd in biological tissue was 20315 ppm. In the case of gadolinium + biological tissue, the factor increase in absorbed dose due to the presence of the heavy element compared to biological tissue is can define.

3. The ability of Gd contrast agent to increase deposited energy.

The computational expression for dose enrichment factor (DEF) takes on a different form depending on the incident X-ray nature, that is, the form of the expression is different for monoenergetic sources and spectral continuous beams [16]. The DEF for monoenergetic source is given as follows:

$$\text{DEF} = \frac{k_{\text{Gd}} \cdot \left( \frac{\mu_{\text{en}}}{\rho} \right)^{\text{Gd}} + (1 - k_{\text{Gd}}) \cdot \left( \frac{\mu_{\text{en}}}{\rho} \right)^{\text{b.t.}}}{\left( \frac{\mu_{\text{en}}}{\rho} \right)^{\text{b.t.}}}$$  \hspace{1cm} (1)

($\mu_{\text{en}}/\rho)^{\text{Gd}}$ - mass absorption coefficient of photon radiation for Gd; ($\mu_{\text{en}}/\rho)^{\text{b.t.}}$ - mass absorption coefficient of photon radiation for biological tissue; $k_{\text{Gd}}$ - Gd content in biological tissue.

The variation of this factor as a function of the energy of the incident photon is illustrated above for 20315 ppm Gd (fig.2) For this heavy element, the maximum deposit of energy occurs for photons of 60 keV, and for 20315 ppm value the DEF is equal 4.12.

![Figure 2](image-url)  

**Figure 2.** The factor of increased energy deposition due to the introduction of 20315 ppm Gd into biological tissue for photons of energy between 1 and 1000 keV.

For X-ray tube radiation, the DEF is calculated as follows [16]:
\[
\text{DEF} = 1 + \frac{k_{\text{Gd}}}{\int \frac{E_{\text{max}}}{E=0} \Psi'(E) \left( \frac{\mu_{\text{en}}}{\rho} \right)_{\text{Gd}} dE} 
\frac{E_{\text{max}}}{E=0} \Psi'(E) \left( \frac{\mu_{\text{en}}}{\rho} \right)_{b.t.} dE
\]

(\mu_{\text{en}}/\rho)^{\text{Gd}} - mass absorption coefficient of photon radiation for Gd; (\mu_{\text{en}}/\rho)^{b.t.} - mass absorption coefficient of photon radiation for biological tissue; \(k_{\text{Gd}}\) - Gd content in biological tissue. \(\Psi'(E)\) – is the differential of photon energy flux, and the limits of integration correspond the maximum and minimum energies of the source.

In the works [17] the results of photon spectrum - \(\Psi(E)\) modelling for 100, 150, 200 kVp X-ray tubes were presented. For these calculated photon spectra the DEF values are defined using (2). Various ionizing radiation sources can be considered for DEF investigation. Such as I-125, Yb-169, Au-198, Ir-192 [18-19] brachytherapy sources commonly used in radiotherapy, and Am-241, Cs-137 also evaluated. The DEF calculations are summarized in Table 2.

**Table 2. Photon radiation sources resulting in DEF.**

| Photon sources | Half Life     | Energy, keV (Intensity, %) | DEF   |
|----------------|--------------|----------------------------|-------|
| I-125          | 59.39 d      | 35.49 (6.63)               | 2.86  |
| Am-241         | 432.2 y      | 26.34 (2.31)               | 2.75  |
|                |              | 59.54 (35.92)              | 4.04  |
|                |              | 63.12 (44.05)              | 4.01  |
|                |              | 109.78 (17.36)             | 1.76  |
| Yb-169         | 32.02 d      | 177.21 (22.32)             | 1.36  |
|                |              | 197.96 (35.93)             | 1.26  |
| Ir-192         | 73.83 d      | 205.79 (3.34)              | 1.21  |
|                |              | 295.96 (28.72)             | 1.09  |
| Au-198         | 2.69 d       | 411.8 (95.54)              | 1.03  |
| Cs-137         | 30.05 y      | 661.66 (84.99)             | 1.01  |
| X-ray tube     |              |                            |       |
| 100 kVp        |              |                            | 3.39  |
| 150 kVp        |              |                            | 3.29  |
| 200 kVp        |              |                            | 3.05  |

Overall, this analysis of DEF calculations indicates that for 20315 Gd contrast agent in biological tissue will provide the dose enhancement. It is also interesting to note the magnitude of the dose enhancement for the various sources. Based on the sources considered high degrees of dose enhancement occur for Am-241, Yb-196, and 100kVp. The maximum DEF is only slightly less for 150 and 150 kVp sources. These differences will become important with high concentrations of contract agent in tumor.

For deeper understanding of energy deposition is needed to discuss the photoelectron pathways. In addition to the reasons mentioned in the preceding paragraph, an additional argument argues in favor of irradiation from energy 67 keV of gadolinium medium is that at this energy, the photoelectron K has an initial kinetic energy of about 17 keV, which corresponds to a path of the electron in water, calculated under the assumption of continuous deceleration, of 6 micrometers (see fig. 3). This is therefore of the same order of magnitude as the cell diameter. The photoelectron, by its systematic ejection after a photoelectric event, is therefore a good candidate for the transport of irradiation.
energy. The interesting to favor irradiation for therapeutic purposes at energies higher than 200 keV for Gd contrast agents seems the no justified.

![Figure 3](image)

**Figure 3.** The mean path of electron in water as a function of its initial kinetic energy [20].

4. Discussion

In [21-22] studies were to evaluate and compare the radiosensitizing properties of gadolinium nanoparticles (NPs) with the gadolinium contrast agent (GdCA) Magnevist. The radiosensitizing properties were determined following either low energy synchrotron irradiation or high energy gamma irradiation of F98 rat glioma cells exposed to ultrasmall gadolinium NPs (GdNPs, 3 nm) or GdCA. Clonogenic assays were used to quantify cell survival after irradiation in the presence of Gd. Radiosensitization was demonstrated with both of these agents along with X-irradiation. At the same concentration (2.1 mg/mL), GdNPS showed a more important effect than GdCA. The maximum sensitization-enhancement ratio at 4 Gy (SER4Gy) was observed at 65 keV irradiation energy, both for the nanoparticles and the contrast agent: SER4Gy = 2.47±0.30 and 1.41±0.15, for GdNPs and GdCA, respectively. At high energy (1.25 MeV), radiosensitization was observed with GdNPs only: SER4Gy = 1.59±0.13 and 1.02±0.13, for GdNPs and GdCA, respectively. The radiation dose enhancements were highly “energy-dependent” for both agents. Photoactivation to be the primary mechanism by which Gd contrast agents can function as radiosensitizers. Other mechanisms, such as alterations in the cell cycle and proliferation explain the enhanced radiosensitizing properties of GdNPs. In conclusion of this study provides strong evidence that GdCA or GdNPs both be used for radiation dose-enhancement therapy. Their biological distribution at the cellular scale will be the key factor for providing large dose-enancements and will determine therapeutic efficacy.

It should be noted various new nanomaterials [23] have emerged as an exciting tool in cancer theranostic applications due to their multifunctional properties and intrinsic molecular properties aiding effective diagnosis, imaging, and successful therapy. However, chemically synthesized nanoparticles have several issues related to the cost, toxicity and effectiveness that restrain its clinical translation.

5. Conclusion

It notes that low-energy photons with energy \( \leq 20 \text{ keV} \) are strongly absorbed by a biological tissue and will create additional radiation damages without leading to a significant increase in DEF. An increase in DEF is observed when the photon energy is higher than the ionization energy of the K-shell of the Gd atom, indicating that the photoelectric effect plays a major role in radiosensitization, which is highly energy dependent. For the presence of 20315 ppm Gd contrast agent (radiosensitizer) in biological tissue the dose enrichment factor is maximum DEF = 4.12 at photon irradiation energy 60
keV. And at photon energies ≥ 300 keV, the dose increase factor DEF in biological tissue in the presence of Gd will be ~ 1.0.

This effect was calculated for gadolinium-based contrast agent dose injections on small animals. This calculation for doses of clinical injections must be more detailed. To further optimize the effect of this binary radiation therapy with X-ray it would be interesting to study in more depth the mechanisms of heavy element action at monochromatic irradiation with ideal energy, and time dependency of contract agent presence in the tumor to obtain a maximum lethal effect on the cellular scale. To explain all events (Auger electrons, recombination of charges, re-absorption of fluorescence, photoelectrons) and to predict the consequences of this type of resonant irradiation on cell survival a physical model should be put in place.

As with any type of binary radiotherapy, requiring the presence of a compound in the tumor to produce the desired effect, the precise determination of the quantities of pharmacological agents present at the time of irradiation is the first data essential to the dosimetric planning of the treatment. Knowledge of the magnitude of the effect is the second. These two primary aspects are the necessities of radiosensibilization effect achievement.

The X-ray tube radiation is certainly the ideal tool for studying this therapeutic method and can optimize all involved parameters, and it is interesting for clinical benefits. The presence of heavy pharmacological agents in the tumor would make possible to increase the lethal biological efficiency of this irradiation technique. Finally, apart from X-rays and γ-rays, this type of approach can transpose to other ionizing particles.

References
[1] Smith L, Kuncic Z, Ostrikov K and Kumar S 2012 Nanoparticles in cancer imaging and therapy J. Nanomaterials 7 pages.
[2] Rahman W, Bishara N, Ackerly T, He C, Jackson P, Wong C, Davidson R and Geso M 2009 Enhancement of radiation effects by gold nanoparticles for superficial radiation therapy Nanomedicine 5(2) 136-142.
[3] Carter J, Cheng N, Qu Y, Suarez G and Guo T 2007 Nanoscale energy deposition by X-ray absorbing nanostructures J. Phys. Chem. B 111(40) 11622-25.
[4] Zhang X, Wu D, Shen X, Chen J, Sun Y, Liu P and Liang X 2012 Size-dependent radiosensitization of PEG coated gold nanoparticles for cancer radiation therapy Biomaterials 33(27) 6408-19.
[5] Hainfeld J, Dilmanian F, Zhong Z, Slatkin D, Kalef-Ezra J and Smilowitz H 2010 Gold nanoparticles enhance the radiation therapy of a murine squamous cell carcinoma Phys. Med. Biol. 55 3045-59.
[6] Roux S, Tillement O, Billotey C, Coll J, Le Duc G, Marquette C and Perriat P 2010 Multifunctional nanoparticles: from the detection of biomolecules to the therapy Int. J. Nanotechnology 7(4-8) 781-801.
[7] Liu Y, Zhang P, Li F, Jin X, Li J, Chen W and Li Q 2018 Metal-based NanoEnhancers for Future Radiotherapy: radiosensitizing and Synergistic Effects on Tumor Cells Theranostics 8(7) 1824-49.
[8] Li F, Li Z, Jin X, Liu Y, Li P, Shen Z, Wu A, Zheng X, Chen W and Li Q 2019 Radiosensitizing Effect of Gadolinium Oxide Nanocrystals in NSCLC Cells Under Carbon Ion Irradiation Nanoscale Research Letters 14 328-340.
[9] Gong L, Zhang Y, Liu Ch, Zhang M and Han S 2021 Application of Radiosensitizers in Cancer Radiotherapy Journal of Nanomedicine 6 1083–1102.
[10] Hubbell J and Seltzer S Radiation Physics Division, PML, NIST Standard Reference Database I26 Last Update to Data Content: July 2004.
[11] Abdullaeva G, Kulabullaev G, Kim A, Djuraeva G and Juraeva N 2019 Promising radiosensitizers for photon therapy LXIX International Conference on Nuclear Spectroscopy and Nuclear Structure “Fundamental Problems of Nuclear Physics, Nuclei at Borders of
Nucleon Stability, High Technologies” Dedicated to the International Year of the Periodic Table of Chemical Elements (Dubna, Russia, 1–5 July 2019): Book of Abstracts / Ed. by V. V. Samarin and M.A. Naumenko. — Dubna: JINR 309.

[12] Corde S 2002 Enhancement of the photo-electric effect with pharmacological agents in synchrotron radiation based anti cancer radiotherapy: a methodological study Ph.D. Thesis Joseph Fourier University - Grenoble I France 71-72.

[13] Kim A, Kulabdullaev G, Koblik Yu, Abdullaeva G, Djuraeva G, Salikhbaev U, Saytjanov Sh, Mavlyanov I, Agzamov O, Alimov J, Khodjaeva N and Navruzov S 2014 Gadolinium Visualization in Vivo for Dosimetry in Neutron Capture Therapy Int. J. Nuclear Energy Sciences and Engineering 4(2) 43-49.

[14] Abdullaeva G, Djuraeva G, Kim A, Koblik Yu, Kulabdullaev G, Rakhmonov T and Saytjanov Sh 2015 Evaluation of absorbed dose in Gadolinium neutron capture therapy Open Phys. 13 183–187.

[15] Kulabdullaev G, Kim A, Abdullaeva G, et al. 2019 Preliminary Study of Gadolinium Accumulation in Glial Tumours of Human Brain IOSR J. of Dental and Medical Sciences 18(7) 69-75.

[16] Roeske J, Nuñez L, Hoggarth M, Labay E and Weichselbaum R 2007 Characterization of the Theoretical Radiation Dose Enhancement from Nanoparticles Technology in Cancer Research & Treatment 6(5) October 395-401.

[17] Abdullaeva G, Kulabdullaev G, Kim A and Normatov E 2019 About development of x-ray source for photon activation therapy (in Russian) The bulletin of young scientists 1(3) 11-14.

[18] Nath R, Anderson L, Luxton G, Weaver K, Williamson J and Meigooni A 1995 Dosimetry of interstitial brachytherapy sources: Recommendations of the AAPM Radiation Therapy Committee Task Group No. 43 Med Phys 22 209-234.

[19] Bé M and Chechev V 2013 Recommended standards for gamma ray intensities. Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment Elsevier 157 - 172.

[20] Berger M, Coursey J and Zucker M 1999 ESTAR, PSTAR, and ASTAR: Computer Programs for Calculating Stopping-Power and Range Tables for Electrons, Protons, and Helium Ions (version 1.21), [Online]. Available: http://physics.nist.gov/Star. National Institute of Standards and Technology, Gaithersburg, MD.

[21] Taupin F, Flaender M, Delorme R, et al 2015 Gadolinium nanoparticles and contrast agent as radiation sensitizers Physics in Medicine and Biology 60(11) 4449-64.

[22] Delorme R, Taupin F, Flaender M et al 2017 Comparison of gadolinium nanoparticles and molecular contrast agents for radiation therapy enhancement Medical Physics 44(11) 5949-60.

[23] Madamsetty V, Mukherjee A and Mukherjee S 2019 Recent Trends of the BioInspired Nanoparticles in Cancer Theranostics Frontiers in Pharmacology 10 Article 1264.