Increased Radiation Efficiency by Metal-Based Nanoparticles in Colorectal Cancer Cells

Soraya Emamgholizadeh Minaei[1*], Mahshid Mohammadian[2], Omid Asnaashari[3], Kamal Mostafanezhad[3]**

[1] *Department of Medical Physics and Imaging, School of Allied Medical Sciences, Urmia University of Medical Sciences, Urmia, Iran*

[2] *Department of Clinical Biochemistry, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran*

[3] *Department of Radiation Oncology, Omid Research and Treatment Center, Urmia, Iran*

Received: 14 Jun. 2025; Accepted: 21 Feb. 2026

Abstract- Colorectal cancer (CRC) is diagnosed as one of the most prevalent cancers in the world. The application of radiotherapy in cancer treatment might be limited due to its radio resistance. Specific radiosensitizers are important factors in increasing the radiation therapy (RT) efficiency. In this study, Fe_3O_4@CuS-PEG nanoparticles in combination with the RT were evaluated for the treatment of CRC cells (HT-29 cells). HT-29 cells were treated with 2, 4, and 6 Gy of X-ray irradiation and/or a minimal toxic concentration of Fe_3O_4@CuS-PEG nanoparticles. The cytotoxic effect of various treatments was evaluated by MTT assay. Moreover, the malondialdehyde (MDA) level, superoxide dismutase (SOD) activity, and lactic acid level were assessed in single and combined treatments. Furthermore, the epidermal growth factor receptor (EGFR) gene expression level was measured by Quantitative Real-time PCR. Based on our results, cytotoxicity of Fe_3O_4@CuS-PEG nanoparticles was increased in a dose dependent manner. The nanoparticles were less cytotoxic in the concentration of 5 mg/mL compared to other examined concentrations. According to the results of MTT assay, the viability in the combined treatment groups was significantly lower than that of the single treatment groups. EGFR mRNA expression level was downregulated in radiation+nanoparticles groups in all examined doses of radiation. The level of MDA increased in the combined treatments compared to the alone treatments. Moreover, lactic acid level and SOD activity decreased in double agent combination treatments versus radiation alone. Based on our study, Fe_3O_4@CuS-PEG nanoparticles can be introduced as an effective radiosensitizer agent for targeted treatment of CRC cells. Moreover, combination treatment could efficiently treat cancerous cells and inhibit tumor growth in vitro.

Acta Med Iran 2026;64(5):257-264.
https://doi.org/10.18502/acta.v64i5.22208

Keywords: Colorectal cancer; Nanoparticle; Radiation; Epidermal growth factor receptor

Introduction

Colorectal cancer (CRC) is one of the major types of cancer and the leading cause of cancer-related mortality worldwide (1). Radiotherapy (RT) is considered as a common and effective treatment for cancers (2-4). Indeed, RT is widely used as a single therapy or in combination with other treatments (5). RT applied to >50% of affected cancerous patients as a common therapeutic strategy by utilization of high-energy X-rays or gamma (γ) rays. DNA double-strand breaks and the creation of free radicals induced by radiation are toxic to most cancer cells (6). The slight difference between normal tissues and tumors in their ionizing radiation responses has been an important subject for tumor radiotherapy (7).

RT with high doses has limited due to damage to surrounding normal tissues. Consequently, highly controllable and selective radiosensitizers are instantly required (5). Recently, there has been a remarkable

Corresponding Authors: S. Emamgholizadeh Minaei* and M. Mohammadian**
* Department of Medical Physics and Imaging, School of Allied Medical Sciences, Urmia University of Medical Sciences, Urmia, Iran
Tel: +98 4432752200, E-mail addresses: Minayee.s@gmail.com, Emamgholizadeh.s@umsu.ac.ir
** Department of Clinical Biochemistry, Faculty of Medicine, Urmia University of Medical Sciences, Urmia, Iran
Tel: +98 4432752300, E-mail addresses: clinicalbiochem86@gmail.com

change in the treatment of cancer, from cytotoxic drugs with broad-spectrum effects toward targeted drugs (8).

Nanoparticles (NPs) as radiosensitizer agents in combination with radiotherapy are suggested for the cancer treatment in various studies. Radio sensitization via NPs is considered an innovative strategy for the treatment of tumors (9).

The advances in the labeled radiosensitizers with probes, including contrast agents and radionuclides for computed tomography and magnetic resonance imaging have resulted in the promotion of image-guided RT, and these radiosensitizers have potential for usage as therapeutic agents for the treatment of cancers (10). Metal sulfide nanomaterials (MeSNs) are a new metal-containing nanomaterial, comprised of sulfur compounds and metal ions. It has been found that the MeSNs engineered through specific methods had high biocompatibility and showed exclusive physicochemical properties, such as light conversion, radiation enhancement, immune activation, and Fenton catalysis for cancer treatment (11). It has been indicated that Superparamagnetic iron oxide nanoparticles (SPIONs) increase the radiotherapy effects in numerous studies (9).

Recently, the associated mechanisms for the toxicity of nanomaterials have been evaluated intensively. An essential mechanism of cytotoxicity is the reactive oxygen species (ROS) generation. Indeed, overproduction of ROS could be related to oxidative stress induction, leading to cells don't capable to retain normal physiological redox-regulated functions. This in turn leads to unregulated cell signaling, DNA damage, apoptosis, cytotoxicity, and initiation of cancer (12). The epidermal growth factor receptor (EGFR) has a significant function in tumor progression and resistance to therapies for numerous types of cancers comprising colorectal cancer. Various EGFR targeted therapies are effective as single agents or combined therapies. Due to its important role in cell proliferation and other cellular processes, EGFR is an attractive target for cancer therapy (13).

Objectives

In this study, we evaluated the cytotoxicity and radio sensitizing efficacy of Fe_3O_4@CuS-PEG nanoparticles in combination with radiotherapy on HT-29 CRC cells.

Materials and Methods

Cell culture, treatments, and cytotoxicity effects of nanoparticles

The Fe_3O_4@CuS-PEG nanoparticle was obtained from Parseh Company (Tehran, Iran). HT-29 CRC cells were obtained from the Pasteur Institute (Tehran, Iran). The HT-29 cells were seeded in DMEM medium (Gibco), which were supplemented with 10% fetal bovine serum (FBS) and1% penicillin-streptomycin antibiotic. All cells were kept in 5% CO2 at 37° C in an incubator. The MTT cytotoxicity assay was carried out using the MTT assay kit. A total of 96-well plates containing 1×10^4 HT-29 cells were treated with X-ray irradiation (2, 4, and 6 Gy) and varying concentrations (range 0.5-5 mg mL^{-1}) of Fe_3O_4@CuS-PEG nanoparticles. After 24 h of incubation, MTT solution was added to each plate and incubated for 4h, then Dimethyl sulfoxide (DMSO) solution was added. The optical density of samples was measured using ELISA kits at 570 nm. According to the results of MTT assay in different concentrations of Fe_3O_4@CuS-PEG NPs, the dose-response plot was drawn. Based on the results of the dose-response curve, the minimal toxic dose of NPs was selected for combined treatments. In combined treatments, the cultured cells were treated with the minimal toxic concentration of NPs (5 mg/mL) and radiation (2,4, and 6 Gy). The treated cells were incubated for a 24 h time frame and then subjected to MTT.

Therapeutic efficiency of nanoparticles in combination with X-ray irradiation

Determination of lactic acid level

HT-29 cells were treated with the 100 µL of Fe_3O_4@CuS-PEG NPs suspension wat the concentration of 5mg/mL for 24h. Then the cells were treated with X-ray radiation at the doses of 2,4, and 6 Gy. After 24h incubation at 37° C, cell suspensions were utilized for the lactic acid measurement. Indeed, the cell supernatants were collected and Lactic acid level was assessed by a lactic acid assay kit (GmbH (Germany) according to the kit procedure. The experiment was performed in duplicate. Wells' absorbance was read with the microplate reader at 543nm as m/dl.

Evaluation of superoxide dismutase (SOD) activity and malondialdehyde (MDA) level

In this method, cells were seeded for 24 h before treatments and then exposed to Fe_3O_4@CuS-PEG nanoparticle and X-ray irradiation, as described above. The supernatants of each treated and untreated cells were utilized for measuring SOD activity by colorimetric assay (ZellBio, Germany).

The absorbance rate was read at two times, including 0 and 2 min at 420 nm by an ELISA reader. SOD activity was calculated in all wells using the following formula:

SOD activity (U/mL)=(Vp-Vc)/ (Vp) ×60
Vp=OD sample 2 min - OD blank 2 min
Vc=OD sample 0min-OD blank 0min

MDA level as a lipid peroxidation marker was measured by colorimetric assay (ZellBio, Germany). In this way, HT-29 cells were cultured and after 24 h of treatments with irradiation and Fe_3O_4@CuS-PEG NPs (as described), cell supernatants of each sample were collected for measuring MDA level according to the kit instructions.

Quantitative real-time polymerase chain reaction (qRT-PCR) analysis

After 24h of treatments, in all treated and untreated wells, cells were trypsinized and collected. Total RNA was extracted from cells by RNA extraction kit (Gene all, South Korea) according to the kit instructions. The single-strand complementary DNA (cDNA) was synthesized using the Prime Script cDNA synthesis kit (Takara Bio Inc., Japan). Real-time PCR was carried out on an ABI Plus one system using SYBR® Premix Ex Taq™ (Takara Bio Inc., Japan). The reaction conditions were pre-denaturation at 94° C for 3 min; followed by 40 cycles of denaturation at 94° C for 10s, annealing at 58° C for 30s, and extension at 72° C for 20s.

The mRNA gene expression of EGFR was normalized to the B-Actin gene and calculated by the $2^{-\Delta\Delta Ct}$ method.

Statistical analysis

Data were presented as mean±standard deviation (SD). Differences between groups were determined using the one –way ANOVA (analysis of variance). A value of $P \leq 0.05$ was considered statistically significant.

Results

Cytotoxicity effects of nanoparticles

In this presented study, we evaluated the combinatorial effects of Fe_3O_4@CuS-PEG nanoparticles with X-Ray irradiation (2, 4, and 6Gy) for enhancing the radiation efficiency. The cytotoxicity effects of Fe_3O_4@CuS-PEG NPs were examined by MTT assay in various concentrations to determine the minimal toxic concentration of NPs for combination treatments. Based on the results of MTT assay, the dose-response curve of Fe_3O_4@CuS-PEG nanoparticles was plotted. As can be seen in Figure 1, the toxicity of NPs was decreased in a concentration-dependent manner. Based on the dose-response curve analysis, the 5mg/mL concentration of Fe_3O_4@CuS-PEG NPs was selected for combination treatment with X-ray radiation (2, 4, and 6 Gy).

The cytotoxic effects of NPs and radiation are presented in Figure 2. As shown in Figure 2, the cell viability rate was decreased in single treatments with 2, 4, and 6 Gy X-ray radiation versus the control sample. While, in the single treatment with Fe_3O_4@CuS-PEG NPs, there was no significant differences with the untreated control cells. In all double combinatorial cases, including Fe_3O_4@CuS-PEG in combined with 2, 4, and 6 Gy doses of radiation, there were a significant decrease in cellular viability compared to the control cells ($P<0.05$).

Therapeutic efficiency of nanoparticles in combination with X-ray irradiation

Determination of lactic acid level

According to our findings, which are presented in Figure 3, there was a significant decrease in lactic acid levels of HT-29 cells treated with NPs + 2, 4, and 6Gy of ionizing radiation compared to the untreated control cells ($P<0.05$). Moreover, significant lower levels of lactic acid were observed in all double agent treatments, including NPs+IR (2 Gy), NPs+IR (4 Gy), and NPs+IR (6 Gy) than that of the related single treatments ($P<0.05$).

Evaluation of superoxide dismutase (SOD) activity and malondialdehyde (MDA) level

The results of the SOD enzyme activity have been shown in Figure 4A. Data from SOD activity assessment in HT-29 cells treated with 0, 2, 4, and 6Gy ionizing radiation showed that there were no significant decreased in SOD activity level in single treatments of radiation in all examined doses ($P>0.05$). Whereas, SOD enzyme activity was reduced significantly in all double combination treatments compared to untreated cells. In the HT-29 cells treated with the combination of Fe_3O_4@Cus-PEG NPs and X-rays (at the 2,4, and 6 Gy), a remarkable decrease in the SOD enzyme activity level were presented compared to the single treatments ($P<0.05$).

Figure 4B displayed that MDA levels in the cells treated with double treatments of 0, 2, 4, and 6Gy ionizing radiation and NPs were increased compared to the control samples ($P<0.05$). Moreover, MDA level were increased in double agent treatments, including NPs+IR (2, 4, and 6Gy) versus the related single treatments ($P<0.05$).

Quantitative real-time polymerase chain reaction (qRT-PCR) analysis

In order to evaluate one of the possible mechanisms of the efficiency of X-ray and NPs, the EGFR mRNA

expression levels were studied using the qRT-PCR analysis. As shown in Figure 5, the mRNA expression levels of EGFR gene were decreased in an X-ray dose-dependent manner. Indeed, the EGFR mRNA expression levels were decreased in single treatments of radiation (2, 4 and 6 Gy doses) versus the untreated control sample (P<0.05). There was no significant difference in EGFR mRNA expression level between the cells treated with Fe_3O_4@Cus-PEG NPs at a concentration of 5mg/mL and the control sample (P>0.05). As described in Figure 5, HT-29 cells treated with ionizing radiation (at all doses) and Fe_3O_4@Cus-PEG NPs exhibited a significant decrease in the expression level of the EGFR gene in comparison with the cells treated with radiation alone (P<0.05). The EGFR gene expression levels in the cells treated with NPs+6Gy, NPs+4Gy, and NPs+2Gy were decreased significantly compared to the control group (P<0.05).

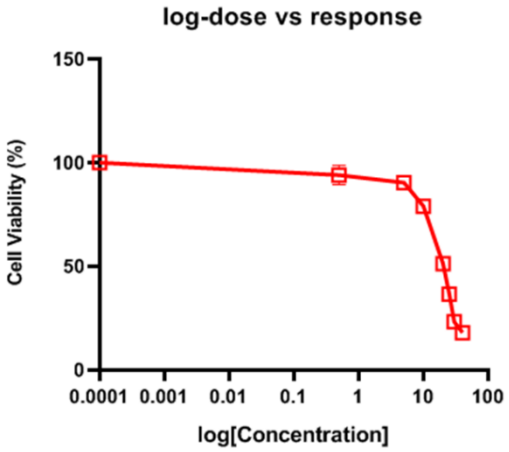

Figure 1. The dose-response curve of Fe_3O_4@CuS-PEG nanoparticles. Data were presented as mean±SD

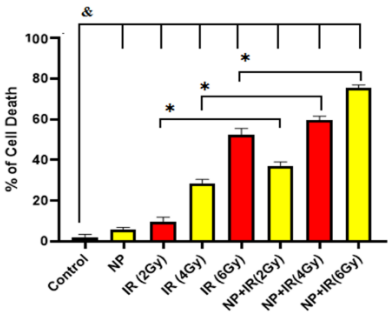

Figure 2. The cell death of HT-29 cells treated with Fe_3O_4@Cus-PEG nanoparticles and X-Ray irradiation with different doses for 24h by the MTT method. Data were presented as mean ± SD. *; significant differences with related single treatments. &; significant differences with the untreated control sample

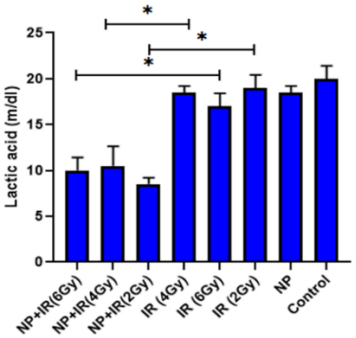

Figure 3. Effects of Fe_3O_4@Cus-PEG nanoparticles in combination with radiation on HT-29 cells in the Lactic acid level. Data were represented as mean±SD of three independent experiments. Statistical significance was showed with *P<0.05

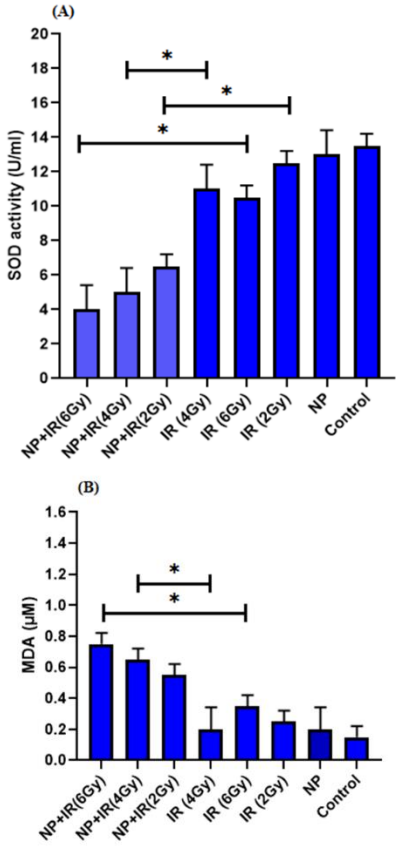

Figure 4. Effects of Fe_3O_4@Cus-PEG nanoparticles in combination with radiation on HT-29 cells on the (A) superoxide dismutase (SOD) activity, (B) malondialdehyde (MDA) level. Data were represented as mean ± SD of three independent experiments. Statistical significance was showed with *P<0.05

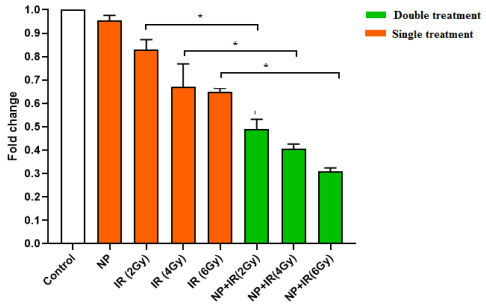

Figure 5. The Epidermal growth factor receptor (EGFR) gene expression level in HT-29 cells after various treatments was determined by the qRT-PCR technique. Data were normalized to beta-actin and presented as mean fold change ± SD. *P<0.05, significant respect to the single radiation treatments

Discussion

Cancer has been the furthermost importance among other diseases. It has been indicated that tumor growth is homeostatic balance disruption that regulates proliferation and apoptosis (14,15). The resistance to various treatment options is not commonly exclusive. It seems that the cancer could be resistant to several treatments. Nonetheless, the associated mechanisms are intricate (15,16). Certainly, targeted therapy in various types of cancers, such as solid tumors is planned as a hopeful effective therapy (16,17).

This study aimed to investigate the therapeutic performance of Fe_3O_4@Cus-PEG NPs in combination with ionizing radiation on HT-29 cells for detecting the therapeutic efficiency and some possible related

mechanisms. Our study demonstrated that Fe_3O_4@Cus-PEG nanoparticles at low concentrations were biocompatible against HT-29 cells. This can be in the result of functionalization of nanoparticles with PEG polymer shield (18).

Evaluation the cytotoxicity effect of different treatments indicated that various combinations of ionizing radiation with Fe_3O_4@Cus-PEG NPs could represent cell death induction, and induced significant cell toxicity. In our study, the efficacy of radiation therapy was improved by Fe_3O_4@Cus-PEG NPs as a possible radiosensitizer agent.

To assess underlying mechanisms mediating the Fe_3O_4@Cus-PEG NPs radio sensitization, the EGFR gene expression rate, SOD activity, MDA level, and lactic acid level were examined. As illustrated in Figure 5, the combination cases showed better results in decreasing EGFR gene expression level as one of the related tumor growth factors in comparison with single radiation treatments. According to a similar study, silver graphene quantum dots in combination with radiation and 17-AAG decrease the EGFR protein expression, which was in accordance to our data (19).

Treatment of cells with Fe_3O_4@Cus-PEG NPs and radiation lead to decrease in lactic acid levels than the radiation treated cells (Figure 3). Figure 4 showed that combination treatment with Fe_3O_4@Cus-PEG NPs and ionizing radiation (at each doses) could induce significantly higher cytotoxicity than that of the single treatment under the same doses of radiation ($P<0.05$). During combination treatment, SOD activity decreased compared to the single radiation treatment. Moreover, MDA level detection assay proved that MDA level as a lipid peroxidation marker increased in double therapies versus radiation alone.

In the study by Gao *et al*., DOX-loaded Fe_3O_4@mSiO_2-FA-CuS-PEG nanocomposites displayed a synergistic effect of photothermal therapy and chemotherapy in HeLa cells under irradiation (20). Meidanchi et al. demonstrated that Mg(1-x) CuxFe2O4 SPM NPs enhanced the cytotoxicity effects of ionizing radiation and could be introduced as a radiosensitizer agent (21).

Here, as well as reviewing recent investigations on RT with organic, inorganic, and biomimetic nanomaterials, the related mechanisms of NPs radiosensitization were assessed, that it may be associated with studying novel directions for the radiosensitizers' clinical translation (22).

It has been indicated that the biological effects of ionizing radiation are related to DNA double-strand break and oxidative stress that can cause cell death (23). Our results showed an improved therapeutic efficiency and synergistic effect for combination treatment. In fact, this synergistic effect could be due to the simultaneous radio sensitizing effects of Fe_3O_4 and CuS nanoparticles. Because of the small size of NPs, these agents can definitely accumulate in the tumor area by passive targeting device known as enhanced permeability and retention (EPR) effect (24). Due to the high accumulation of nanoparticles inside cancer cells, the Compton interaction of ionizing radiation with iron and copper nanoparticles increases, leading to enhanced production of high-energy secondary electrons in cancer cells and generation of free radicals, which can cause cell damages (25,26). Moreover, copper and magnetite nanoparticles can increase the reactive oxygen species formation by the Haber–Weiss and Fenton reaction (7,27).

Similarly, in the study by Rashid *et al*., SPIONs, AuNPs, BiNPs, and PtNPs had radiosensitization effects in human colon carcinoma cells (HCT-116 cells), which were related to the increased level of ROS produced by respective NPs. These data showed the potential of using high Z metallic NPs for radiation therapy, which may enhance the effects of cancer therapies (28).

In our study, the remarkable decrease in cell survival through the combination of radiotherapy with minimal toxic concentration of Fe_3O_4@Cus-PEG nanoparticles showed the effectiveness of the applied radiotherapy. The results of radiation and NPs combination therapies involving in vitro study offer the validation of the efficiency of these combined cases in CRC treatment.

These data could demonstrate increase in cytotoxic effects in CRC cells although it must be noted that further studies should be conducted in vitro and in vivo to understand the related mechanisms of radio sensitization.

With regard to the efficiency of NPs and radiotherapy, these results offer an approach to an effective treatment option with only minimal side effects.

Ethics Approval

The protocol was approved by the Ethics Committee of Urmia University of Medical Sciences (IR.UMSU.REC.1399.387).

Funding

This work was supported by Urmia University of Medical Sciences under grant No. 2830.

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