Asian Journal of Applied Science and Technology (AJAST)
(Open Access Quarterly International Journal) Volume 2, Issue 1, Pages 77-86, 2018

Radiosensitizers and Radioprotectors for Effective Radiation Therapy– A Review

T.Ruba[1] and Dr.R.Tamilselvi[2]

[1]*Department of Electronics and Communication Engineering, Sethu Institute of Technology, Tamilnadu, India. Email: rubasuresh20@gmail.com*
[2]*Department of Electronics and Communication Engineering, Sethu Institute of Technology, Tamilnadu, India. Email: rts.ece@gmail.com*

Article Received: 22 September 2017 *Article Accepted: 25 December2017* *Article Published: 12 January 2018*

ABSTRACT

Radiation therapy uses ionizing radiation to shrink tumors and kill cancer cells. There are different types of radiations used for cancer treatment such as X-rays, gamma rays, and charged particles. Radiation therapy kills cancer cells by damaging their DNA (Deoxyribonucleic acid). There are different types of radiation therapy for different malignancies. Radiation therapy can also deteriorate the normal cells, leading to side effects. Radioprotectors are compounds that are designed to reduce the damage in normal tissues caused by radiation. They are mostly antioxidants which should be present before or at the time of radiation. Other agents, termed Radiosensitizers may be used to minimize toxicity even after radiation has been delivered. These compounds are used to increase the sensitivity of the tumor cells during irradiation. The aim of this paper is to critically review the available compounds used as radiosensitizers, radioprotectors and antioxidants for different types of cancers.

Keywords: Radiation therapy, Radiosensitizers, Radioprotector and DNA.

1. INTRODUCTION

The goal of radiation therapy is to achieve maximum tumor cell killing while minimizing injury to normal tissues (therapeutic ratio). Local tumor failure is the cause of 40% to 60% of cancer deaths and may occur in 60% to 80% of cancer patients at the time of death. The objective of successful radiation therapy is to maximize the radiation damage in tumor cells and at the: same time minimizes the same in normal cells. This may be possible either by better localization of radiation dose or by using differential radioprotectors for normal cells and/ or radiosensitizers of tumor cells [1]. Clinical use of radiation therapy is given in figure1.

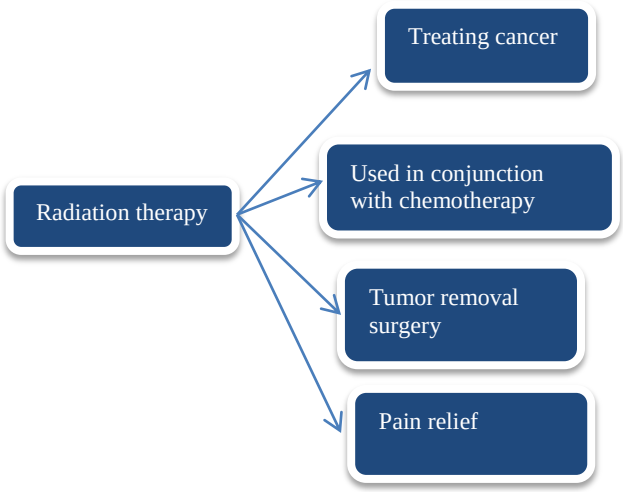

Fig. 1. Clinical use of Radiation therapy

 Online ISSN: 2456-883X Impact Factor: 1.805 Website: www.ajast.net

Radiation therapy is the most effective tool against treatment of cancer. High doses of radiations are used in radiation therapy to halt growth of tumor. Ionizing radiation (IR), like X-rays and gamma-rays, is commonly used for the treatment of cancer because it has the ability to pass through tissues and can break chemical bonds and help in the removal of electrons from atoms to get ionized. The ionized ions as a result damage cancer cells. Cancer cells are not killed immediately by ionizing radiation; in fact, substantial time is required for killing of cancer cells. Ionizing radiation can decrease the signs and symptoms induced by a growing tumor.

To increase the effect of therapies, ionizing radiation is often given before, during, and even after the surgery. The exposure of ionizing radiation can be external and internal. External beam radiation like X-rays or γ-rays targets the particular part of the cancerous patient. Therapies of internal radiation have neutrons, electrons, protons, α or β particles, and carbon ions in which solid or liquid radiation is placed within the body. The use of ionizing radiation to kill cancer cells biologically depends on the kind of radiation being given, amount of dosage, rate of fractionation, and the organ to be targeted [2]. Although radiotherapy is one of the most effective treatments for cancer, still a large number of patients had radioresistance of their cancers. Ionizing radiation if given alone is found to be more effective against few cancers like non-small cell lung cancer, cervical cancer, larynx cancer, skin cancer, head and neck cancer, prostate cancer, and lymphomas, but it is not found to be effective for the cancers like breast cancer, glioblastoma, advanced non-small-cell lung cancer, bladder cancer, and soft tissue carcinoma, maybe because of intrinsic radioresistance of cancer cells [3].

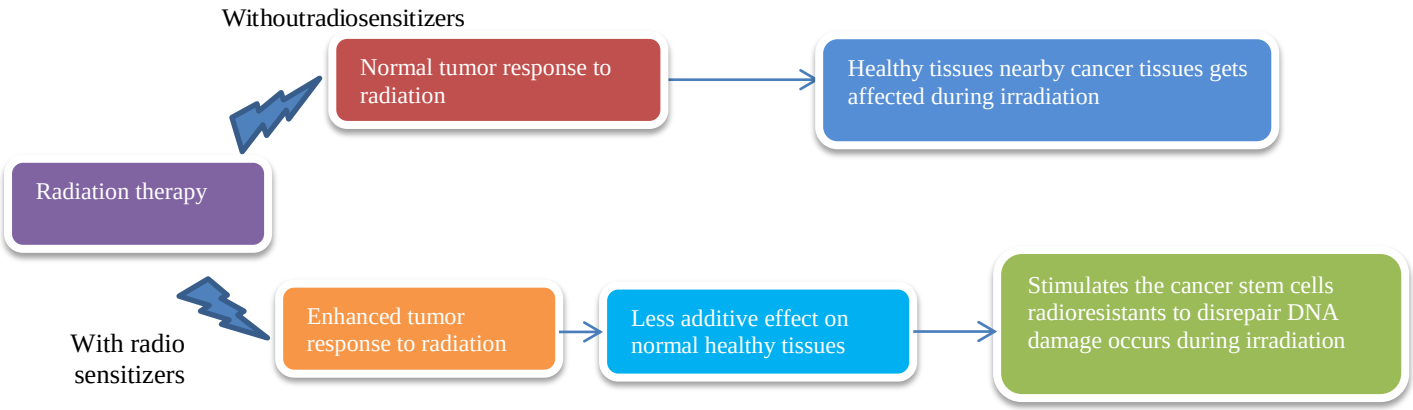

Fig. 2. Effect of Radiation therapy with and without the use of radiosensitizers

A radiosensitizer is a drug that makes tumor cells more sensitive to radiation therapy. These compounds apparently promote fixation of the free radicals produced by radiation damage at the molecular level. The mechanism of action is similar to the oxygen effect, in which biochemical reactions in the damaged molecules prevent repair of the cellular radiation damage. Free radicals such as OH+ are captured by the radiosensitizers, rendering the molecules incapable of repair [4]. Radioprotectors are compounds that are designed to reduce the damage in normal tissues caused by radiation. Antioxidants may also acts as radioprotector and they must be present before or at the time of radiation for effectiveness. Other agents, termed mitigators, may be used to minimize toxicity even after radiation has been delivered [5].

2. RADIOSENSITIZERS

Radiotherapy commonly affects DNA; mainly it leads to DNA double strand break. So, to target clinically developed DNA double strand break (DSB) repair pathways, many radiosensitizing agents have been formulated. Effect of radiation therapy with and without the use of radiosensitizers is given in fig2.

The HR inhibitor nucleoside and base analogs like gimeracil, gemcitabine, pentoxifylline, TAS-106, and caffeine. The HDAC inhibitor PCI-24781, the HSP90 inhibitor 17-allylamino-17-demethoxygeldanamycin, the tyrosine kinase inhibitors imatinib and erlotinib, and the proteasome inhibitor MG132 all target HR repair pathway to radiosensitize cancer cells [6].2

2.1 Radiosensitizer for cervix cancer

Cancer of the uterine cervix is the most common form of malignancy in women. The use of additional therapy with an enzyme preparation along with radiotherapy will reduces side effect. Trypsin, Chymo trypsin and papain have been used for the reduction of toxicity due to the radio therapy treatment for Cervix cancer. Enzyme therapy along with radiotherapy may effectively reduce the early complications [7].

2.2 Radiosensitizer for prostate cancer

The role of natural food products in prevention of prostate cancer has been confirmed in recent epidemiological studies; however, the mechanism of chemoprevention by the dietary constituents largely remains unknown. Curcumin, the yellow pigment and active component of turmeric (Curcuma longa), exhibits chemopreventive and growth inhibitory activity against several tumor cell lines. Curcumin augments (TNF-alpha-related-apoptosis-inducing-ligand) TRAIL-mediated apoptosis in androgen-sensitive prostate cancer cells. The induction of apoptosis by combined curcumin and TRAIL treatment involves the activation of initiator/effectors caspases (caspase-8, caspase-9 and caspase-3), cleavage of proapoptotic Bid, and the release of cytochrome c from the mitochondria. Thus, combination of TRAIL with curcumin, a pharmacologically safe compound, may provide a more effective adjuvant treatment for prostate cancer [8].

2.3 Radiosensitizer for breast cancer

Esape from apoptosis is considered to be one of the major mechanisms underlying the resistance of many types of tumors against radiotherapy and chemotherapeutic agents. Hence, it is believed that increasing the apoptotic response of tumor cells would help to develop more effective clinical treatment of the disease. Therefore, the inducers of apoptosis would potentially contribute towards an effective strategy to achieve improved treatment of cancer patients. During our quest for naturally occurring anticancer compounds, adiethylether derivative (D7) synthesized from diospyrin was found to be more cytotoxic than the parent compound in human breast cancer cell line [9].

2.4 Betulinic acid

In recent years, plant polyphenols like betulinic acid have received attention for their influence on initiation and progression of cancer. Betulinic acid is active against head and neck cancer, melanoma, medulloblastoma, neuroblastoma, glioblastoma and glioma. Betulinic acid has no antiproliferative effect on normal derma fibroblasts and lymphocytes. In combination with irradiation it has been shown to have an additive effect on growth inhibition in melanoma cells and head and neck squamous cell carcinoma (HNSCC) cells. They proposesbetulinic acid as a radiosensitizers on sequential irradiation in head and neck cancer cell lines [10].

2.5 Ellagic acid (EA)

EA (Ellagic Acid) is a plant-derived polyphenol, possessing antioxidant, antiproliferative, and antiatherogenic activities. Plants produce EA to protect themselves from microbiological infection and pests. EA has also been said to reduce heart disease, birth defects, liver problems, and to promote wound healing. EA seems to possess some anti-cancer properties which have been seen in a variety of cells and tissues like breast, liver, lung, colon etc. The mechanism of action of EA involving ROS, cell cycle arrest, apoptosis and activation of signalling molecular cascade as observed in radiosensitization of some tumor cell lines. EA is proven as an effective inducer of apoptosis and hence a potential therapeutic in the treatment of cancer cells [11]. Some other radiosensitizers are listed in Table1.

3. RADIOPROTECTORS

Radioprotectors are agents that are used to reduce the deterioration of normal cells during irradiation. Antioxidants may also acts as radioprotector and they must be present before or at the time of radiation for effectiveness. Radioprotectors are chemical compounds that protect the non-tumor (normal) cells from radiation during radiotherapy [5].Some of the Radioprotectors are discussed below. The effect of radiation therapy with and without the use of radioprotector is given in fig3.

3.1 Amifostine: Amifostine (WR-2721) is one of today's most widely studied protectors. Amifostine selectively protects a broad range of normal tissues, including the oral mucosa, salivary glands, lungs, bone marrow, heart, intestines, and kidneys. Amifostine also protects against the cytotoxic effects of chemotherapeutic agents. It offers significant protection against the nephrotoxicity, ototoxicity, and neuropathy associated with cisplatin and hematologic toxicity associated with cyclophosphamide [12].

3.2 Nitroxides: Amifostine is the only radioprotector currently in clinical use. A number of other compounds are in various stages along the pathway of clinical development as radiation protectors. Nitroxide is a most promising agent for future use as radiation protectors.

4. ANTIOXIDANTS AS RADIOPROTECTORS

With the understanding that free radicals perpetuate a significant amount of the damage caused by ionizing radiation, multiple vitamin antioxidants have been tested as a method to reduce the toxicity of radiotherapy. Antioxidant compounds such as glutathione, lipoic acid, and the antioxidant vitamins A, C, and E have been evaluated in this context. In general, the efficacy of these naturally available agents as radioprotector is less than synthetic agents. One of the major concerns with the use of supplemental nutritive antioxidants or other antioxidants during the course of radiotherapy is the possibility of tumor protection through non selective free radical scavenging.

The use of antioxidant vitamins, such as alpha-tocopherol and beta carotene, during the course of radiotherapy was associated with evidence of poorer tumor control in randomized trials [12], [13]. When discussing antioxidants as radioprotectors, it is worth mentioning the use of superoxide dismutase (SOD) as a method to prevent radiotherapy-induced toxicity. Ionizing radiation results in the formation of superoxide radicals that are highly reactive and potentially damaging to cells. SOD is an enzyme that is naturally present in human cells. It catalyzes the conversion of superoxide to oxygen and hydrogen peroxide and functions as an antioxidant during normal conditions and after radiation. SOD uses gene therapy in order to increase the levels of SOD in tissues which are going to be irradiated to prevent or decrease radiation-induced mucositis, esophagitis, pneumonitis, and fibrosis in animal models [14].

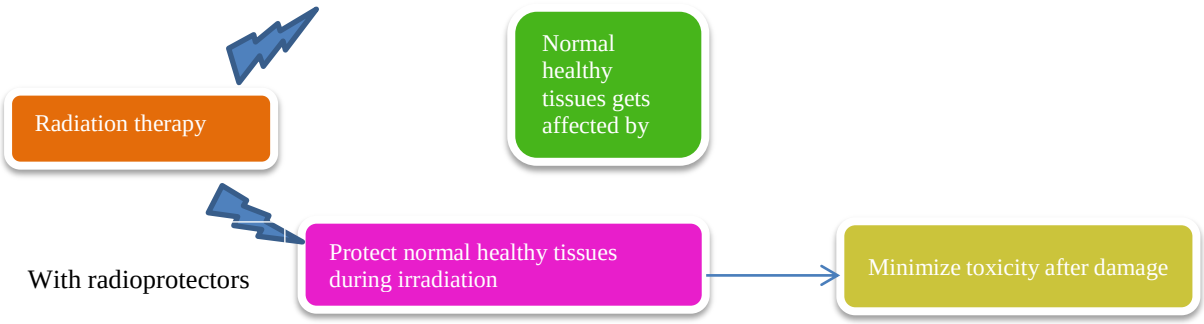

Fig. 2. Effect of Radiation therapy with and without the use of radioprotectors

4.1 Melatonin

Although Melatonin acts as an antioxidant, it also acts to increase the expression of antioxidant enzymes such as SOD and glutathione peroxidase.

4.2 Vitamin E (Alpha-tocopherol)

Vitamin E (VE) provides oral mucosal protection in patients with irradiated cancers of the head and neck. VE has a potential protective effect on the oral mucosa of irradiated patients with tumors of the oral cavity and oropharynx [15].

5. ANTIOXIDANTS AS DEFENCE AGAINST ROS/RNS MEDIATED ENVIRONMENTAL POLLUTION

Many environmental pollutants are sources of several reactive species (RS). RS is a collective term that includes both oxygen radicals and other reactive oxygen and nitrogen species (ROS/RNS). Some of the free radicals are hydroxyl (OH*), superoxide (superoxide (O2 *-), Nitric oxide (NO*), thyl (RS*) and peroxyl (RO2 *) radical. The term reactive oxygen species (ROS) is often used to include not only free radicals but also the non-radicals (e.g.O2, ONOO-, H2O2, O3) [16].

There is strong evidence that RS is involved in oxidative/nitrosative stress (O/NS) as a common mechanism by which several environmental pollutants induce damage. Oxidative stress is a consequence of an increased generation of RS and/or reduced physiological activity of antioxidant defences against RS. Environmental pollutants stimulate a variety of mechanisms of toxicity on molecular level and oxidative stress seems to be the common denominator leading to the damage to cellular membrane lipids, DNA, and proteins [17], as well as modulation of antioxidant enzymes. When the antioxidant defence in the human body becomes overwhelmed, oxidative stress to the cellular components often occurs, inducing inflammatory, adaptive, injurious, and reparative processes [18].

The air pollution results the following health issues such as minor irritation of the eyes and the upper respiratory system to chronic respiratory disease, lung cancer, heart and vascular disease, and death. Oxygen could be presented as the leading air pollutant ion regard to oxidative stress formation. The diatomic molecule of oxygen contains two uncoupled electrons and can therefore undergo reduction, yielding several different oxygen metabolites, which are collectively called ROS (Reactive Oxygen species). The main site of intracellular oxygen consumption is Mitochondria and also the main source of ROS formation. Once ROS are produced, they are removed by cellular defences which include the enzymes superoxide dismutase (Mn-SOD, Cu/Zn-SOD, and extracellular (EC)-SOD), catalase, glutathione peroxidase, peroxiredoxins, and the nonenzymatic antioxidants, like glutathione (GSH), thiore-doxin, ascorbate, α-tocopherol, anduricacid.

Clinical studies imply that eating a diet rich in fruits, vegetables, whole grains, legumes, and omega-3 fatty acids can help humans in decreasing oxidative stress and postponing the incidence of degenerative diseases[19],[20].

Tobacco smoke is one of the most common air pollutants and generates high amounts of various ROS/RNS. The protective effects of vitamin C, glutathione, and other antioxidants, mainly as quenchers of ROS/RNS will reduces the cigarette induced oxidative stress was [21], [22].

6. NANO PARTICLES AS RADIOSENSITIZERS AND RADIOPROTECTORS

Radiationtherapy (RT) is an approved, most widely used strategy for the treatment and control of cancer progression but its successful application solely depends on the radiosensitivity of tumor cells and tolerance of normal tissue. To overcome this, very often radiation therapy is combined with radiosensitizing agents. Recently, due to the advancement in the field of nanotechnology, metal nanoparticles have been discovered as the novel radiosensitizers such as gold nanoparticles (GNPs).In contrast, some nanoparticles of noble metals like Platinum nanoparticles (nano-Pts) act as Radioprotectors and inhibit radiation-induced cell death [23].

6.1 Gold Nanoparticles as Radiosensitizer

Recently, GNPs have been the subject of intensive biomedical research due to their unique physicochemical properties including surface Plasmon resonance (SPR) and the ability to bind amine and thiol groups, allowing surface modification and functionalization. Theoretically the radiosensitizing effect of GNPs is based on the concept that high atomic number materials absorb low kilo voltage (kV) X-rays more efficiently and deposit the energy precisely, resulting in the enhanced radiation dose deposition specifically to tumor cells.

When considering sensitizing effects of GNPs, it is important to know the key parameters involved in GNPs-induced radiosensitization such as GNPs size, shape, concentration, surface coating, type of cell line and radiation energy. The GNPs conjugated with polyethylene glycol for stabilization of golgnanosol, were found to sensitize EMT-6 breast carcinoma cells and CT26 colorectal adeno carcinoma cells to various types of ionizing radiation [24].

The radiosensitizing effect of GNPs may be dependent on the various factors. Some parameters are GNPs size, cell type, and surface modifications.

6.2 platinum nanoparticles as Radioprotectors

Name Of The Drug	Therapeutic uses	Suggestions(when to use)
GLEOSTINE	Head and neck cancer	Treatment of patients with primary and metastatic brain tumors following appropriate surgery and/or radiotherapy.
HYDREA	Head and neck cancer	Adjunct with irradiation therapy in locally advanced squamous cell carcinomas of the head and neck, excluding the lip.
TAXOTERE	Head and neck cancer	In combination with cisplatin and fluorouracil: induction treatment of locally advanced squamous cell carcinoma of the head and neck.
ABRAXANE	Breast cancer	Treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy (prior therapy should have included an anthracycline unless clinically contraindicated).
CYCLOPHOSPHAMIDE	Breast cancer	Carcinoma of the breast
ZOLADEX	Breast cancer	Palliative treatment of advanced breast cancer in pre- and perimenopausal women.
ABRAXANE	Respiratory and thoracic cancers (Lung cancer)	First-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.
AVASTIN	Respiratory and	First-line treatment of unresectable, locally advanced, recurrent or metastatic

	thoracic cancers (Lung cancer)	non-squamous, non-small cell lung cancer (NSCLC), in combination with carboplatin and paclitaxel.
GEMZAR	Respiratory and thoracic cancers (Lung cancer)	First-line treatment of inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) non-small cell lung cancer (NSCLC) (in combination with cisplatin).
CISPLATIN	Prostate cancer	Adjunctive therapy for metastatic testicular tumor.
PREMARIN	Prostate cancer	Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only)
XOFIGO	Prostate cancer	Treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.
INTRON A	Melanoma and other skin cancers	Malignant melanoma.
ODOMZO	Melanoma and other skin cancers	Treatment of adults with locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation, or those who are not candidates for surgery or radiation therapy.
ZELBORAF	Melanoma and other skin cancers	Treatment of unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Limitation of use: not for treatment of wild-type BRAF melanoma.
AFINITOR	Brain cancer	In adults and children with tuberous sclerosis complex (TSC) for the treatment of subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected.
AVASTIN	Brain cancer	Glioblastoma, as a single agent for patients with progressive disease following prior therapy.
COSMEGEN	Bone and connective tissue cancer	In combination with other chemotherapy and/or multi-modality treatment regimen for childhood rhabdomyosarcoma, Ewing's sarcoma. As a component of regional perfusion, for palliative and/or adjunctive treatment of locally recurrent or locoregional solid malignancies.

Platinum has the similar atomic number as gold, and high atomic number materials are known to enhance the biological effects of radiation. Platinum-based drugs have long been used to treat various types of cancers. However, nanoparticles of some noble metals, including platinum (Pt), act as reducing catalysts due to the large surface area of smaller particles. These nano-Pts have gained much attention due to the fact that they use as an antioxidants to scavenge ROS persistently and catalytically in living organisms. In fact these nano-Pts can scavenge superoxide anions (O2-) and peroxides (H2O2), indicating that they can act as superoxide dismutase (SOD)/ catalase mimetics. The nano-Pts suppressed the LPS (LipoPolySaccharide)-induced production of both superoxide and peroxides in macrophages. This is consistent with the reported ability of nano-pts in scavenging ROS, and thus ROS suppression by the pre-treatment of the nano-Pts resulted in the inhibition of inflammatory response. Therefore the presence of nano-Pts in a biological system can induce various effects depending upon the stimulus, and combination of nano-Pts (SOD/ catalase mimetics) may result in the reversal of cell killing effects induced by different treatment modalities, such as radiation [25].

The nano-Pts were also being able to induce lethal DNA damage and P53-mediated growth arrest. Furthermore, FePt @ CoS2 yolk shells nano-Pts were found to be more potent in killing HeLa cell than cisplatin [26]. Although gold and platinum are noble metals, they usually considered as the efficient ability for radiosensitization and reducing catalyst due to the large surface area of smaller particles.

Other than these radio protectors and radiosensitizers, there are also some of the drugs which can be used during irradiation. Some of the drugs and their therapeutic uses were given in Table II [27].

7. CONCLUSION

In conclusion, radiosensitizers and Radioprotectors have a special role in the treatment of malignancies by radiotherapy. Every agent has its own application, mode of action, and adverse effects. The novel agents are exhibiting promising results. In majority of instances, the success rate of radiotherapy is related to radiosensitizers and the patient's quality of life is dependent on the radioprotectors. Also there is substantial evidence that environmental pollution increases oxidative stress which causes the formation of ROS (Reactive Oxygen Species) and that dietary antioxidant supplementation may play a role in neutralising the effects of pollutants. The research on nanoparticles as radiosensitizers and radioprotectors is going on and in future this may reduce the cancer death.

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