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Radiation induced therapeutic effects in cancerous and tumor cells: A review

Abstract

Present review article describes use of radiation and radionuclides on cancer and cancer cell therapeutics. It also sketches out cumulative effects of radiation exposure received by the patients during cancer diagnostics. Though, in cancer therapeutics a selected and permissible dose is provided in several cycles to ablate the neoplastic cells and improve the condition of patient, but radiation harms surrounding cells and imparts negative effects on biology of cells. Ionizing radiation (IR) promotes cancer cell death through cytotoxicity. This article emphasizes both remedial effects and biological effects of radiation and radio-resistance in cells. It suggests safe use of radionucleides by encapsulating them in nanomaterials so as to use it alternate to chemotherapy to destroy various cancer types to enhance the survival of normal cells. This article explains effect of ionizing and non-ionizing radiation on cellular metabolism and genetics.

Keywords: radiotherapy, cancer, ionizing and non-ionizing, dose level, cancer therapeutics, occupational, accidental effects, and DNA damage

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Introduction

Most cancers arise after genes have been altered by cancer-causing chemicals, called carcinogens, or by errors in their transcription and repair. Even if genetic damage occurs in a single somatic cell, this cell division will produce more efficient cells. In normal tissues, cell proliferation is a tightly controlled process. Growth-promoting factors are released in a tightly controlled manner to ensure that cells only proliferate to replenish tissue. In this way, cancer cells gain the ability to proliferate continuously. This ability leads to an expansion of the cancer cell population. Cancer occurs when the mechanisms that maintain the normal rate of proliferation malfunction and cause excessive cell division. Loss of cellular regulation that gives rise to most or all cancers is due to genetic damage often caused by tumor-promoting chemicals, hormones, and sometimes viruses. Oncogenesis, also known as carcinogenesis or tumorigenesis, is the formation of cancer in which normal cells are transformed into cancerous cells. This process is characterized by changes at the cellular, genetic and epigenetic levels and abnormal cell division. Most cancer deaths are caused by invasive and rapidly growing metastatic tumors.

More generally, a series of mutations occurring in many genes produces an increasingly rapidly proliferating cell type that escapes the limits of normal growth, providing the opportunity for additional mutations. The cells also acquire other properties that give them an advantage, such as the ability to exit the normal epithelium and stimulate the growth of blood vessels to take in oxygen. Affected cells will normally pass the damage on to their daughter cells, creating a copy of the damaged cells. However, rarely a mutation of a single gene leads to the development of cancer. Eventually, the cell clone turns into a tumor. In some cases, cells from the primary tumor migrate to new sites, where they form secondary tumors, a process known as metastasis. Cancer cells have evolved mechanisms to escape this tight control. Cancer cells upregulate growth-promoting pathways while down regulating growth inhibitory and cell death pathways.[1]

Oncogenes and cancer

Gene mutations cause uncontrolled cell proliferation caused by stimulation of signals that give cancer cells the ability to proliferate indefinitely. Mutations in three broad gene classes are associated with cancer. Proto-oncogenes usually promote cell growth. Mutations turn them into oncogenes, the products of which are hyperactive in stimulating growth. Oncogenic mutations usually result in increased gene expression or production of an overactive gene product. Tumor suppressor genes normally inhibit growth, so mutations that inactivate them lead to improper cell division. A third class of genes often linked to cancer, called genome maintenance genes, are involved in maintaining the genome's integrity. When these genes are inactivated, cells acquire additional genetic changes at increased rate including mutations that cause the deregulation of cell growth and proliferation and lead to cancer. Many of the genes in these three classes encode proteins that help regulate cell proliferation (i.e., entry into and progression through the cell cycle) or cell death by apoptosis; others encode proteins that participate in repairing damaged DNA.[2] In spite of the major cause of cancer is genetics mainly aberrant growth of cells due to defaulted gene function and immortality of cells. Cancer results from failures of the mechanisms that usually control the growth and proliferation of cells. It is an established fact that environmental factors affect the genome and alter the structure and function of proteins, with cumulative effects on gene expression and also in behaviour. These fundamental changes can be studied in terms of the epigenetic behaviour of drugs in biochemical, biological and pharmacological studies. It is reported that epigenetic effects are cumulatively imposing breast, liver, and bowel cancer and causing high morbidity and mortality throughout globe.

Use of radiation for cancer treatment

Radiation is used for both therapeutic and diagnostic purposes.[3] It is an immediate destroyer of cancer cells and is used to remove cancerous growths/sites.[4] It is used as an alternative to chemotherapy to destroy cancer cells and improves the survival of normal cells by restoring the cell's microenvironment.[5] Radiation is a major carcinogen that induces neoplastic changes in cells (Figure 1). Despite the harmful effects of radiation on body tissues, low-level radiation exposure induces protective mechanisms by activating physiological functions during the early stages of radiation damage. However, while limited, low-dose radiation is used to destroy squamous cell carcinoma, bone tumors require high-dose radiation in targeted

treatment strategies.[6] Radiation beams damage cancer cells, helping to reduce cancer masses and helping tumor patients recover. There are different types of radiation exposure of the human body, depending on the type of radiation emitted by the radiation source. Various salts with predominantly gamma-type wave emission have been offered for therapeutic purposes (Figure 1). There are two main types of radiation: ionizing radiation and non-ionizing radiation. Ionizing radiation contains sufficient energy during interaction with atoms to remove strongly bound electrons from their orbits and charge or ionize the atoms. The most common types of ionizing radiation are alpha particles, beta particles, gamma rays, and x-rays. Diagnostic applications of ionizing radiation in medicine include the use of X-rays and radioisotopes in imaging (Figure 1). Hematologic cancer measures in patient treatment courses include extracorporeal UV blood irradiation, intravenous laser blood irradiation, and venous blood laser irradiation.

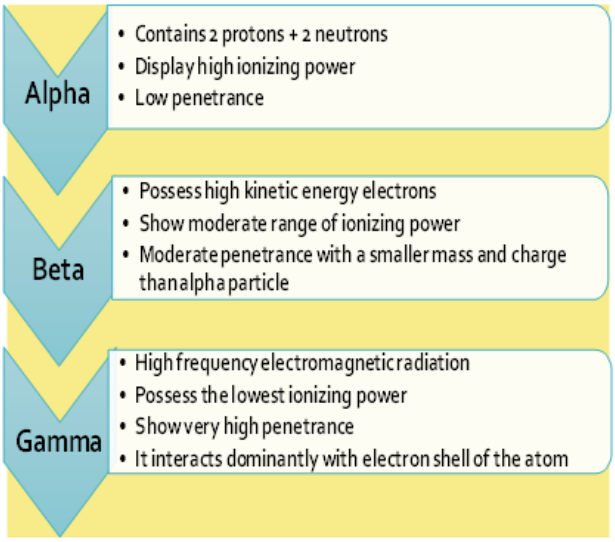

Figure 1 Showing radiation types and its properties.

Radiation therapy is therefore one of the most common and effective treatments for a wide range of tumors. However, radio tolerance of cancer cells remains a major limitation for the application of radiotherapy. Ionizing radiation also induces signaling in target cells. New innovations, such as the study of sensitization targets and the development of radiosensitizers to improve radiotherapy outcomes, could revolutionize this method. Radionuclides are used to deliver cytotoxic doses of radiation to diseased cells/tissues. Radio sensitivity, especially reactive oxygen species, DNA damage response signals, and many cellular targets that can influence the tumor microenvironment are of great importance in cancer therapy. Selective delivery of radiation dose to target tissue is required. Its administration should be protective and non-invasive so that immediate and late side effects can be minimized. Besides ablation of cancer cells by using radiation, programmed cell death is also suitable way to attack cancer and cancer cells.[3]

For cancer treatment, multiple cycles of radiation therapy are given to remove tumor cells and improve the patient's condition. Radiation eradicates tumour cells in large numbers and minimally kills normal cells. Radiation shows therapeutic effects and penetrates deep into the body layers and destroys toxic aggregates, reducing oxidative stress and protecting cells from aberrant metabolic damage.[7] But it imposes a series of epigenetic effects like DNA methylation, histone modification, chromosome remodelling, RNA modification mainly non-coding RNA.[8] Ionizing radiation (IR) promotes cancer cell death through the creation of cytotoxic DNA lesions, including single strand breaks, base damage, cross links, and double strand breaks.[9] It causes direct induction of DNA damage and its cellular consequences.

Radiation also generates autoimmune encephalomyelitis and neuro-immune diseases in experimental rats.[10] Radiation also imposes pathogenesis like lesions, coagulation necrosis and obstructions in blood flow and causes infarction.[11] It also affects melatonin, a vital natural neuro-hormone that regulates our circadian rhythms and acts as a powerful antioxidant, anti-depressant and immune system enhancer. The quantity of radiation reaches the brain and alters patho-physiology of central nervous system (CNS) and generates delayed effects such as demyelination, gliosis and necrosis. Radiation also absorbed through radioreceptors and induces various syndromes and neurological diseases.[12] Further, high dose of radiation severely affects daily sleep/wake cycle, hormone production and immune system activity. It also affects blood pressure and interferes with daily activity cycles either directly or indirectly through heart rate cycle, metabolic rate, body temperature regulation, and the autonomic nervous system. It also causes significant changes in molecular and cellular mechanisms and causes allergic encephalomyelitis.[13] Several treatments are prevalent to control cancer growth, but few have the desired success. Adjuvant therapy is also used to kill cancer cells that may remain after primary treatment to reduce the chance of the cancer returning.[14] Adjuvant radiation therapy is used to treat people with pancreatic cancer. It completes stage II invasive ductal carcinoma, stage III adenocarcinoma, stage T4 carcinoma, and stage N1 adenocarcinoma stage,[15] of the head of the pancreas. Common adjuvant treatments include chemotherapy, radiation therapy, and hormone therapy. Palliative care can help relieve signs and symptoms caused by the side effects of treatment or by the cancer itself. Surgery, radiation therapy, chemotherapy, and hormone therapy can be used to relieve symptoms. Other drugs can relieve symptoms such as pain and shortness of breath. Radiation therapy is a form of adjuvant therapy used in many cancer treatment protocols. Radiation therapy uses powerful beams of energy, such as X-rays or protons, to kill cancer cells. Radiation therapy can be performed by applying an external beam of radiation or placed inside the patient's body, known as brachytherapy. Radiation therapy uses alpha, beta, beta/gamma, or electron emitters. In general, alpha therapy is highly selective for cancer treatment because it has few side effects (Figure 1). The advantage of radionuclide therapy is that it delivers a high absorbed dose to the target tumor without affecting the surrounding normal tissue.[16] Additionally, the selectivity of radionuclide therapy makes it useful for the treatment of systemic malignancies such as bone metastases.

Cancer cells are also destroyed by using cryolysis

To do this, a needle (cryoprobe) is inserted through the skin and directly into the cancerous tumor. Inject gas into the cryoprobe to freeze the tissue. The tissue is then thawed. The freezing and thawing process is repeated multiple times during a single treatment session to kill cancer cells. Radiofrequency energy passes through the needle and heats the surrounding tissue, killing the surrounding cells. In particular, proton therapy is used to treat breast cancer.[17] Reduce radiation dose to non-target structures while optimizing target coverage. Radiolabeled peptide therapy is also being used to target cancer cells.[18] The combination of radiotherapy, immune modulators, and immune checkpoint blockade has shown promising results in targeting metastatic tumors, particularly through systemic responses. In most cases, telomerase inhibitors can be very effective treatments for cancer. In a short period of time, the progression of cancer can

be stopped by systematic treatment such as surgery, radiation, and drugs. This article describes therapeutic use of radiation for cancer therapeutics. For delivery of radionuclides functional carriers are needed which may control the pharmacokinetics of radionuclides and exert excellent therapeutic effects against cancer. In addition, various beneficial molecules such as chemotherapeutic drugs and contrast agents can be loaded onto the same material for combination therapy and therapeutic studies.

Dose determination

Radioisotopes used in cancer therapy include chromium phosphate P32, sodium iodide I 131, Sr-89, Sm-153, and Re-186. Strontium-89 is injected into a vein. A typical dose is 4 millicuries, depending on age, height and blood count. Repeated doses may be required. The usual dose of Samarium Sm 153 Lexidronam is 1 millicurie per kilogram of body weight (0.45 millicuries per pound) injected slowly intravenously. Repeated doses may be required. Sodium Iodide I 131 Sodium Iodide I 131 is taken orally as a capsule or as a solution. The usual dose to treat thyroid cancer is millicuries, depending on age and height. Dosing can be repeated. Some important radionuclides used in cancer therapy are, for example, B. chromium phosphate P32 for lung, ovarian, uterine, and prostate cancer, sodium iodide I 131 for thyroid cancer, samarium Sm 153 is used for cancerous bone tissue and sodium phosphate P 32 is used for cancerous bone tissue and other types of cancer. Usual dosages range from 1 to 5 millicuries (Table 1 and 2).

Table 1 Showing radio-nuclides, decay and half life

Radionuclides	Type of decay emission	Half- life
^{32}P	Beta	14.26 Days
^{89}Sr	Beta	50.53 Days
^{90}Y	Beta	64.10 Hours
^{131}I	Beta	8.02 Days
^{223}Ra	Alpha	11.44 Days
^{177}Lu	Beta	6.73 Days

Table 2 Showing various radionuclides

Radionuclides	Therapeutic effects
^{131}I labelled with Sodium Iodide (^{131}I-NaI) (Radioactive Iodine Therapy)	Graves Diseases ,Solitary hyper-functioning nodules, Toxic multi-nodular goitre
Strontium – 89 (^{89}Sr)	Bone metastasis
^{153}Sm	Bone metastasis
^{153}Sm-EDTMP	Bone pain palliation
^{90}Y-octreotide (Acts by binding on Somatostatin receptor)	Neuroendocrine tumours

Two terms are mainly used when specifying Gy: 'radiation dose' and 'absorbed dose', and when specifying GBq, the period 'recreational dose'. Radiation doses are provided in various Phase I, II, and III testing phases before becoming standard of care. Dosimetry of radionuclide therapy is important for the administration and assessment of radiation effects.[19] Individual dosimetry is also considered to enumerate individual patient biological effects, such as tissue radio-sensitivity, dose rate, detailed radioactivity distribution within organs, and cycle therapy regimens.[20] Accurate dose assessment during radionuclide therapy is therefore essential to optimize therapeutic efficacy at the target site and minimize radiation exposure to surrounding normal tissue.[21] Quantitative single-photon emission tomography (SPECT) and positron emission tomography (PET) are the most widely used methods of tailored radiotherapy (Table 1 and 2).[22]

In SPECT extracorporeal UV blood irradiation, intravenous laser blood irradiation, and supravenous blood laser irradiation is used to control blood cancer. Radiation primarily binds to peptide-bound receptors and lodges in the blood; and set inside bone marrow in the extracellular space[23] and causes toxic effects and reducing tolerance.[24] Imaging techniques and radiolabeled mAbs are used to treat cancers of red bone marrow.[25]

Occupational exposure: Radiation exposure causes many clinical injuries to the body's organs and cells. Various blood biomarkers, immunological, molecular and biophysical markers are used to diagnose radiation-related effects. Direct exposure to radiation comes from work in laboratories, industry, and nuclear power plants. Even after taking protective measures, occupational radiation exposure penetrates the skin when hospital nursing staff goes to treat patients. In radionuclide therapy, tumor DNA repair occurs concomitantly with sub-lethal damage as the dose rate decreases. Patients are cumulatively exposed to high doses during diagnosis by PET/SPECT/CT/MRI, and patients receive cumulatively high doses. EBRT interferes with DNA damage repair, tissue regrowth, tumor re-oxygenation, and cell cycle redistribution. Repeated clinical use of radiation has long-term effects, including carcinogenesis and blood-brain barrier penetration. Even low-dose radiation therapy produces a bystander effect.[26] Natural radiation raining down from space also affects the nervous system of spaceflight pilots (Table 1 and 2).[27]

Radiation therapy is a widely accepted method and a major modality of cancer treatment. WBRT is used to terminate brain metastases and shows varying efficacy in combination with neuroprotective agents or alone. Radiation also destroys the blood-brain barrier, so it is also used to treat brain tumors. More specifically, radiotherapy alters endothelial barrier function such as transendothelial electrical resistance (TEER), morphological effects, localization of adhesion and cell-associated proteins, and permeability of molecules across the endothelial barrier. . Therefore, combination therapy of temozolomide and Herceptin enhances anti-tumor efficacy and enhances mouse survival. Also, insoluble radioactive substances are absorbed only in very small amounts. They are cleared fairly quickly directly from the respiratory and gastrointestinal tracts. But soluble substances pose problems. Their diagnosis is therefore of great importance to reduce deaths from high levels of radiation exposure.[28]

Radionuclides delivery methods: Nanostructures (lipid nanoparticles, multilayered materials, etc.) have been synthesized for the safe and targeted specific delivery of encapsulated radionuclides. In addition, adsorption methods such as inorganic nanomaterials are considered preferable for obtaining stable therapeutics. These methods can reduce α-emitter shedding and increase daughter radionuclide retention at the tumor site. In particular, several β-emitter labeled nanomaterials have been used for multimodal therapy to overcome the limitations of monomodal therapy. In fact, some therapeutic combination strategies yield remarkable synergistic effects. Therapeutic beta-emitting radioisotopes are found in a variety of organic, inorganic, and hybrid forms in nanomaterials. Therefore, stable incorporation of α/β-emitters into nanostructures and precise delivery to tumor target sites are prerequisites for effective cancer therapy and toxicity reduction.

Radionuclides and nanomaterials should be designed with high loading capacity for therapeutic radioisotopes and containing multivalent cancer-targeting molecules. These functional carriers can control the pharmacokinetics of radionuclides and show excellent therapeutic effects. Further research should therefore focus on synthesizing radiolabeled nanomaterials with better radiochemical

stability and desirable pharmacokinetic and clearance profiles to minimize radiation exposure in normal tissues. Improvements in optimized radiochemical procedures and comprehensive validation of the efficacy and toxicity of radiolabeled functional nanomaterials in various animal disease models will lead to the development of useful therapeutic radiopharmaceuticals. Nanostructured materials with nanoscale dimensions have ushered in a new generation of radionuclide generators. These are microstructural materials that exhibit enormous surface-to-volume ratios, altered physical properties, tailored surface chemistry, favourable absorption properties and enhanced surface reactivity.[29] Nanomaterials have a potential role in the development of a new generation of radionuclide generators for broader applications in both diagnostics and therapeutics in nuclear medicine. Drugs loaded with the finest nanomaterials are being used to improve the treatment of tumor patients. These nanomaterials have proven to be more efficient and reliable tools for improving the bioavailability of gene or drug delivery systems.[30] Similarly, inhaled fluorescent magnetic nanoparticles increase drug distribution in the mouse brain, whereas silver nanoparticles (Ag-NPs) interact with brain microvasculature and induce blood-brain barrier inflammation increases the permeability of primary microvascular endothelial cells in the rat brain.

Liposomal formulations i.H. Lipoplatin™ and Lipoxal™, and carboplatin are used to alleviate his F98 malignant glioma in Fischer rats. These liposomal formulations showed moderate drug accumulation in tumor cells, greatly reducing toxicity and allowing better utilization of the anticancer activity of radionuclides. Lipoplatin™ and Lipoxal™ liposomes show similar potency to carboplatin, but accumulate in brain tumors and show better therapeutic efficacy.[31] Therefore, to reduce toxicity, platinum drugs are encapsulated in liposomes for controlled drug delivery administered intravenously, intraarterially, or in combination with disruption of the blood-brain barrier. According to Taira et al., a similar therapeutic effect was observed with chemotherapy combined with cisplatin, vinblastine, and bleomycin (PVB therapy). PVB chemotherapy with cisplatin is well tolerated and exhibits sensitizing and antitumor activity.[32] However, it reduces permeability across the blood-CSF barrier and can be used to treat germ cell tumors that often spread to the cerebrospinal fluid. PVB (cisplatin-vinblastine-bleomycin) therapy is used to optimize radiochemical processes, and reduces the efficacy of nuclear medicine and their toxicity. This leads to the development of useful therapeutic radiopharmaceuticals. Anticancer drugs are useful in the treatment of brain tumors, but their efficacy is limited at subtherapeutic concentrations due to reduced penetration of the blood-brain barrier (BBB). Effective chemotherapeutic agents for primary systemic tumors have limited access to brain metastases due to the blood-brain barrier (BBB).[33] Resection of malignant intracranial germ cell tumors such as embryonic carcinoma, endodermal sinus tumor and choriocarcinoma presents extreme challenges in the pediatric age group due to the assimilation of high radiation during radiotherapy. Therefore, the intra-arterial route is used to temporarily open the blood-brain barrier with mannitol. Similarly, increased fluorescein transport also manifests as a size-dependent increase in BBB permeability that has been found to correlate with immunotoxicity severity. Radiation therapy does not always work synergistically with immunotherapy. The immunostimulatory effect of radioimmunotherapy should be maximized. Application of new technology could be a powerful weapon for improving the efficacy of radioimmunotherapy.

Radiolabeled peptides are used to terminate neuroendocrine malignancies. They exhibit rapid and much better tissue penetration, low antigenicity, convenient production and systemic clearance.[34-38] The RUNX3 protein plays an important role in her TGF-β signalling pathway involved in inhibiting tumor growth and apoptosis. For therapeutic purposes, additional cell blockade induced by 5-aza-CdR during the G2/M phase is achieved by irradiation. By increasing RUNX3 expression, TLR9 signalling activation improved radiosensitivity in lung cancer, and 5-aza-CdR was an option in this process.[39] This therapy is used because various peptide receptors over-expressed on tumor cells are a promising therapeutic strategy. Receptor expression is therefore used to selectively deliver radiation to target tumors by sparing normal tissues.

MicroRNAs are classified as small non-coding RNAs that post-transcriptionally regulate the expression of target genes and are involved in oncogenesis and cancer resistance to therapy. miRNAs as promising predictors and therapeutic targets for personalized radiotherapy in lung cancer.[40] Current strategies targeting the TGFB1 pathway in the prediction of radiation pneumonitis and the TGFB1 pathway in lung cancer radiotherapy may provide potential targets for lung cancer therapy.[41]

Radiopharmaceutical or radioactive tracers: Radioactive substances, so-called radionuclides (radiopharmaceuticals or radiotracers), are absorbed by body tissues. However, they exhibit long-term toxicity and reduced excretion from the body. For diagnostic purposes in clinics and nuclear medicine hospitals, radionuclides are produced in nuclear reactors, cyclotrons, etc. Technetium-99 is the most commonly used diagnostic radionuclide, accounting for 67.3% of CNEN's total revenues in 2017. Besides 99mTc, there were 131I (13.7%), 67Ga (2.9%), 177Lu dot tatate (2.9%) and 18F-FDG (1.1%). more commonly used (Table 1).

90Y-labeled somatostatin analogues (high-energy β-emitters) are effective in treating larger tumors, and 177-Lu-labeled somatostatin analogues (low-energy β-emitters) are effective in treating tumors of various sizes with heterogeneous receptors. It is known to be effective in treating small tumors.[42] Other peptides currently under investigation, some with promising results, are 188Re-P2045 and the 90Y-αvβ3 antagonist 19 (Table 1). Several different types of radionuclides are available. Forms of the elements technetium, thallium, gallium, iodine, and xenon are used to treat various types of cancer. More specifically, chromium phosphate P32 is used for lung, ovarian, uterine, and prostate cancer. Sodium iodide I 131 is used for thyroid cancer and Samarium Sm 153 for treatment of cancerous bone tissues. A variety of important radionuclides are used for diagnostic and therapeutic purposes. More precisely, 90Y, 131I, 153Sm, 166Ho, 177Lu, and 188Re) are currently produced by nuclear reactors. Cyclotrons can produce a variety of radionuclides, but may have better therapeutic applications.[43,44] Therefore, for global radiotherapy, a stable and reliable supply of medical radionuclides for long-term standard care must be ensured (Table 2).[45-48]

Radiotherapy of various cancer types

Radiation therapy (RT) is used to stop cancer cells from growing by delivering high doses of radiation to kill cancer cells and tumors. Radiosensitizers are used to protect the surrounding tissue.[49] Radiation therapy is also used to control neoplastic growths that occur in the rectum, which is at the bottom of the digestive tract. Rectal cancer is treated with MR-guided neoadjuvant radiotherapy.[50] A combination approach is used to interfere with nasopharyngeal carcinoma (NPC). Stereotactic body radiation therapy (SBRT) is used to treat chronic patients. Other common treatments include surgery to remove the cancer, chemotherapy, and radiation therapy.[51]

Bladder cancer

Bladder cancer is a common type of cancer that begins in cells in the bladder. The bladder is a hollow muscular organ in the lower abdomen that stores urine. Bladder cancer most commonly forms in the cells that line the bladder (urothelial cells). Urothelial cells are also found in the kidneys and the tubes that connect them to the bladder (ureters). Urothelial carcinoma can also occur in the kidneys and ureters, but is more common in the bladder. Most bladder cancers are diagnosed in the early stages when the cancer is treatable. Treatment includes surgery, biologic therapy, and chemotherapy. Radiation therapy is also given, but therapeutic radiation causes radiation sensitization in the patient. It increases the likelihood of radiation-induced heart disease (RIHD).[52] Radiation shows also has late effects[53] and causes cardiotoxicity in lung cancer patients during treatment period. The bladder has poor tumor visualization and variability in bladder size and location both between and during treatments. MRI is used for tumor visualization and local staging.[55] Patients are treated with single-plan whole bladder radiotherapy and dose escalating tumor-focused radiotherapy (DART).[56] In addition, precision medicine radiotherapy is provided for prompt treatment.[57]

Lung cancer

There are two types of lung cancer: non-small cell lung cancer (metastatic NSCLC) and small cell lung cancer.[58] Lung cancer has higher morbidity and mortality than most cancers.[59] SLC solely responsible for 10-15% of all lung cancers and yes, the prognosis is very poor. Causes of lung cancer include smoking, second-hand smoke, exposure to certain toxins, and family history. Treatments vary but include surgery, chemotherapy, radiation therapy, targeted drug therapy, and immunotherapy. The JT-VMAT technique is strongly recommended.[60] Palliative pulmonary irradiation with increased total dose (including up to 30 Gy/10 fractions) improves survival regardless of performance status.[61] Thoracic radiation therapy has become more precise and has reduced risk of serious adverse events due to technical developments (IMRT, image-guided radiation therapy, stereotactic body radiation therapy.[62] Small cell lung cancer.[63] Interleukins at baseline 1b and neutrophil counts, and cytokeratin 19 antigens with initial treatment predicted response to radiotherapy in lung cancer. Baseline angioprotein-1 and hepatocyte growth factor (HGF) were significantly correlated with total tumor volume.[64]

Breast cancer

Breast cancer occurs mainly in women and rarely in men. Breast cancer is the second most common cancer in women after skin cancer. Breast cancer occurs when breast cells grow and divide uncontrollably. It forms a mass of tissue called a tumor. A mammogram can detect breast cancer early, possibly before it spreads. Common treatments include chemotherapy, radiation therapy, hormone therapy, and surgery. Although radiation therapy reduces the absolute risk of dying from breast cancer,[65] exposure to ionizing radiation can cause secondary morbidity, namely cancer of muscle cells or heart damage, leading to the development of coronary artery disease and cardiac mortality.[66,67] Therefore, identifying breast cancer patients at highest risk of radiation-induced cardiac complications is important for developing primary and secondary prevention strategies that may contribute to healthy aging.

Radiation therapy is one of the most important treatments for estrogen receptor-positive (ER+) breast cancer. Breast-linked radiotherapy (IMC) reduces the size of irradiated breast cancers and cancer mortality.[68] A single dose of radiation is given in external beam radiotherapy to the breast for early treatment of breast cancer.[69] Radiotherapy for left-sided breast cancer is very important because the heart is nearby. Therefore, positive airway pressure is offered to reduce cardiac dose to normal tissue in breast cancer radiotherapy and save treatment in left-sided breast cancer patients.[70] However, radiation exposure increases cardiovascular burden after breast cancer treatment.[71] LC20A1 can be used as a prognostic marker to predict the efficacy of radiotherapy in luminal A and luminal B breast cancer.[72] Patients undergoing radiotherapy for breast cancer are psychosomatic and require clinical care, counselling and treatment.[73]

Adjuvant radiation therapy is used after breast-conserving surgery. This is a customized method applied on an individual patient basis.[74] Its success depends on key factors related to breast size, patient lateral position, age, and irradiation dose (i.e., partial breast irradiation) that determines success.[75] Radiation therapy may reduce the risk of local recurrence in elderly patients with early-stage breast cancer.[76]

Radiotherapy is effective for skin cancer,[77] esophageal cancer, oral cancer,[78] and ovarian, endometrial, and cervical cancer. Used to treat gynecologic malignancies associated with , vagina and vulva.[79] Radiation therapy is also used to treat glioblastoma multiforme (GBM). GBM has been improved and can be increased by using high-Z metal nanoparticles (NPs).[80] Adjuvant three-dimensional radiotherapy (3D-CRT) and free-breathing tangential intensity-modulated radiotherapy (t-IMRT) are used to protect the cardiac substructure in left-sided node-negative breast cancer.[81]

Prostate cancer

Prostate cancer is the most common cancer in men. Before that, early detection of treatment is critical to controlling prostate cancer.[82] External beam radiation therapy (EBRT) is an effective curative treatment option for localized prostate cancer. A total of 10-20% of patients develop long-term toxicity after radiotherapy for prostate cancer. Various genetic susceptibility to radiotoxicity have been identified that may help improve risk prediction.[83] Radiation genomics studies are valuable for clarifying radiopathogenic effects.[84] Carbon ion therapy (CIRT) is a useful method that provides clinical benefit to prostate cancer patients.[85] The diagnostic method is magnetic resonance imaging (MRI) using intraprostatic gold fiducial markers (GFM).[86] Modern radiotherapy techniques of intensity-modulated radiotherapy are used to modify risk.[87] Prostate cancer cells become metastatic, altering the organ microenvironment and their interactions. Radiation therapy treatment for prostate cancer has reduced morbidity. In particular, cone-beam CT (CBCT)-based soft tissue matching is used for prostate cancer radiotherapy. Therefore, dose-escalating radiotherapy (RT), intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and hypofractionated radiotherapy have been used to reduce toxicity.[88,89] Similarly, MR-associated OAR-dose reduction leads to less toxicity or greater potential for dose escalation due to patient treatment . Balloons are used to treat rectal cancer and reduce acute toxicity.[90] Preoperative (chemo)radiation followed by complete mesorectal ligament resection is used to treat patients with advanced rectal cancer.[91] Radiation therapy is used to treat gynecological malignancies.[92]

Biological effects of therapeutic radiation exposure: The ionizing radiation used in radiation therapy kills the tumor but affects surrounding normal tissue. However, lung cancer patients undergoing radiotherapy experienced secondary morbidity, both acute and chronic toxicity to normal tissues.[93] Radiation has detrimental effects on heart problems and skin cells.[94] Patients with coronary artery disease are at increased risk of receiving radiation doses to control Hodgkin's lymphoma.[95] Breast cancer treatment increases cardiovascular risk. High doses of radiation damage DNA, causing both single-strand

breaks (SSBs) and double-strand breaks (DSBs). It is very difficult to repair such DNA damage after radiotherapy.[96]Repair of this DNA damage determines the radiotolerance of cancer cells.[97] The combination of IMRT and IGRT significantly reduces acute and late rectal toxicity (Figure 2).[98]

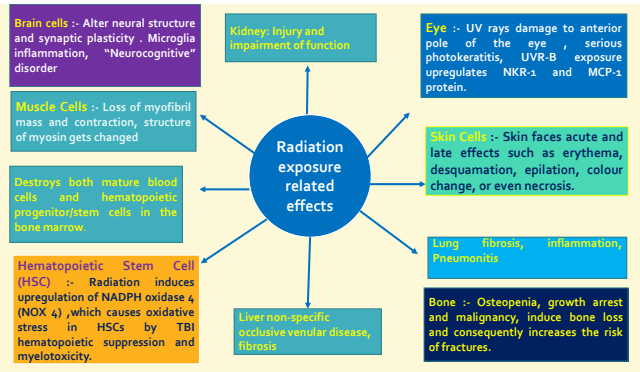

Figure 2 Biological effects of radiation on various organ systems of body.

Radiation therapy is an effective way to treat tumors, but the sensitivity of tumors to radiation varies greatly from patient to patient. However, its success depends on the body's immunity and the patient's resistance to radiation. The skin develops side effects from radiation therapy. Being a sensitive organ, irradiation of the skin causes both acute and late effects such as erythema, desquamation, hair loss, discoloration, or necrosis.[99] Radiation released from a nuclear accident induces hematosuppression and myelotoxicity. Radiation-induced enterobacteriosis may contribute to pelvic radiation disease, including mucositis, diarrhea, systemic inflammatory response, and radiation therapy-related pelvic fatigue in cancer patients.[100] UV and IR exposure cause cancer in humans.[101]

Effect of radiation on glial cells: Therapeutic ionizing radiation massively effect neural stems cells, endothelial and microglial cells. Radiation-induced brain injury (RIBI) activates microglia cellswhich results in progression of chronic neuroinflammation. Radiation also generates late effects and results in brain tumors and imposes neurocognitive disorders.[102] It decreases neurogenesis and differentiation, and causes alteration in neural structure and synaptic plasticity. Cell replacement therapy is used for restoration of memory and cognition deficits.[103] It increases oxidative stress, inflammation and adverse effects in the brain (Table 3). Radiation also affects myofibrils, the contractile organelles from striated muscles (Figure 2).

Table 3 Radiation induced biological effects

Radiation type	Organ system	Biological effect	
		Short term	**Long term**
High-energy X -ray	Integumentary	Erythema, pink coloration, mild edema , itching, burning, mild discomfort, dry desquamation, partial loss of epidermal basal cells, dryness, scaling, peeling, hyperpigmentation, moist desquamation Complete destruction of basal cell layer, blister formation	Pigmentation changes Hair loss Telangiectasia Atrophy Fibrous changes
High-energy X -ray	Digestive	Appetite loss, anemia Diarrhea, Constipation, Nausea and vomiting	Gut squmaous epithelial changes, ulceration
High-energy X -ray	Muscle	Pain	Myofibril break down, slow contraction
High-energy X -ray	Skeletal	Induce bone loss and consequently increases the risk of fractures.	Osteopenia, growth arrest and malignancy
High-energy X -ray	Nervous system	Loss of neural structure and synaptic plasticity, microglia inflammation, sleep disturbance and insominia, nerve pain	Neurocognitive" disorder
High-energy X -ray	Vascular	Death of RBCs, heart attack or stroke	Increase in WBC count, blood cancer
High-energy X-ray	Respiratory	Alveolar inflammation	Lung fibrosis and Pneumonitis
High-energy X -ray	Sensory	Photokeratitis	Loss of vision
High-energy X -ray		Nephrocyte impairment of function	kidney failure
High-energy X -ray	Immune system	Formation of CTL complex, increased infiltration of T lymphocytes ($CD3^+$), natural killer cells ($CD56^+$), and macrophages ($CD68^+$)	Neoplastic activity
Intensity-modulated *radiation therapy*	Endocrine system,	Hypofunction	Metaplasia, cancer and altered bone growth.
Intensity-modulated *radiation therapy*	Reproductive system	Loss of gamete formation	Teratogenesis

Effects of radiation on bone cells

Ionizing radiation is used in radiotherapy to induce bone loss, resulting in an increased risk of fractures due to delayed bone and non-union bone in cancer patients. It also influences the behavior of osteocytes such as bone mesenchymal stem cells (BMSCs), osteoblasts and osteoclasts.[104] Radiation also affects bone formation by osteoblasts (OB) and bone resorption by osteoclasts (OC). IR is used at high doses and has detrimental effects on bone.[105] Bone marrow dysfunction has historically been one of the main causes of morbidity and mortality after ionizing radiation (Table 3).[106]

Effects of radiation on the eye: High doses of ultraviolet (UV) radiation can be harmful to your eyes. Ultraviolet radiation is known to have both beneficial and detrimental effects on the human body. Side effects primarily affect her two target organs, the skin and eyes. Exposure to intense UV radiation has both acute and irreversible effects. It enhances angiogenesis, forming capillaries with structured walls composed primarily of CD34+ endothelial progenitor cells and a basement membrane rich in collagen IV fibers.[107] Exposure to UVR-B causes upregulation of NKR-1 not only in exposed partner eyes in various ocular tissues, but also in unexposed partner eyes. After UVR-B exposure, MCP-1 protein levels are upregulated in exposed eyes, but the contralateral side is unaffected (Figure 2).[108] Radiation has profound effects on cell metabolism, energy supply, and homeostasis, as well as radiation-induced signaling, cell death, and immune responses. Radiation exposure affected skeletal muscle metabolic rate and mitochondrial bioenergetics, and radiation-induced alterations in mitochondrial energy metabolism affected skeletal muscle adenosine monophosphate-activated kinase signaling.[109] IR energy level, dose, and quality influence mitochondria-dependent epigenetic and functional regulation at the cellular and tissue level. IR radiation causes decreased anastasis, increased mitochondria-mediated apoptosis, and an immunogenic (anti-tumor) response.[110]

Radiation exposure affects both gametogenesis and fertilization. More generally, exposure of fertilized eggs to mutagens induces peri-implant death, pangesterone death, fetal and ocular abnormalities. Ionizing radiation affects teratogenicity before gastrulation[111] (Figure 2 photoexposure) and accelerated skin aging (chronic exposure to ultraviolet radiation: UVR). UV-B radiation affects amylase, protease, trypsin, and chymotrypsin activity in UV-B treated fish. T GOT and GPT values were significantly higher in fish exposed for 15 minutes[112] occurs and functions more frequently than radiation-induced damage to Thus, ionizing and non-ionizing radiation affect her ECM of the breast stroma and skin dermis[113] Bone Marrow injuries (Table 3).[114] Induction of this residual BM damage results in hematopoietic stem cell (HSC) senescence. Radiation therapy has been less successful in controlling brain metastases. Tumor radioresistance is induced by circRNAs and used as clinical markers for radiotherapy to explore molecular mechanisms and targets of action (Figure 2).[115]

Irradiation to the breast can cause skin irritation, dryness and discoloration, breast pain, breast swelling due to fluid accumulation (lymphoedema), and hair loss is a common side effect of radiation therapy. However, unlike hair loss during chemotherapy, it only causes hair loss at the treatment site. The most common early side effects are tiredness (fatigue) and skin changes (Table 3). Other early side effects are usually related to the treated area and include hair loss and mouth problems when that area receives radiation therapy. Delayed side effects may take months or years to develop. They can appear in normal tissues in the body that receive radiation. The risk of later side effects depends on the area treated and the radiation dose used. Careful treatment planning can help prevent serious long-term side effects. It is always advisable to consult a radiation oncologist about the risk of long-term side effects. One way to reduce side effects is with the radioprotective drug amifostine. This drug can be used in people with head and neck cancer to reduce oral problems caused by radiation therapy. Fatigue usually worsens as treatment progresses. The stress of commuting daily to illness or treatment can exacerbate fatigue (Figure 2).

Rarely, radiation therapy can change blood cell counts. These blood cells help your body fight infections and prevent bleeding. If blood tests show a low blood count, treatment may be stopped for about a week until the blood count returns to normal. This side effect is more likely if you are also receiving chemotherapy. Radiation to the brain can cause short-term side effects such as headache, hair loss, nausea, vomiting, extreme tiredness (fatigue), hearing loss, skin and scalp changes, memory and speech problems, seizures, and people exposed to radiation. can cause it. The neck may experience side effects such as: sore mouth or throat (or open sores), dry mouth, difficulty swallowing, altered taste, nausea, ear pain, tooth decay, swollen gums, Throat or throat, hair loss, skin texture changes, jaw stiffness (Figure 2) (Table 3).

Radiation and immunotherapy: Cancer patients with little or no pre-existing anti-tumor immunity ("cold" tumors) should undergo an immune check for activation of the innate immune system, including inflammatory signaling, dendritic cell (DC) recruitment and stimulation. It responds poorly to treatment with point inhibitors (ICPIs). Immunoadjuvants are used to induce the immunomodulatory effects of radiotherapy.[116] Immune checkpoint inhibitors (ICIs) target programmed cell death. Protein-1 (PD-1) and programmed cell death ligand-1 (PD-L1) are widely used in the treatment of malignant and metastatic cancers. Radiotherapy can enhance anti-tumor efficacy by following mechanisms and optimization strategies for combined radiotherapy and anti-PD-1/PD-L1 therapy.[117]

A combination of radiotherapy and immunotherapy has emerged as the best method of cancer treatment. Moreover, radiotherapy acts synergistically with immunotherapy to enhance immune responses, inhibit immunosuppression, and/or alter tumor cell phenotypes, making them more susceptible to immune-mediated killing.[118] A major breakthrough in cancer immunotherapy is the discovery of immune checkpoints. It has profoundly changed the landscape of lockdowns, cancer patients, and cancer treatment. Its clinical trials require a combination of radiotherapy and immune checkpoint blockade for breast and other cancers.[119]

It is true that controlled radiation dose ablate cancer cells, but accidental radiation exposure leads to many long-term biological effects and cause cancer. The best example is release of lots of radiation after Chernobyl nuclear accident in April 1986 caused thyroid cancer in children and adolescents. It also imposed lethal physiological and genetic effects on biota, and indirect effects on wildlife.[120] Most post-Chernobyl tumors were found due to a high incidence of chromosomal rearrangements such as RET/PTC. However, point mutations in BRAF and other genes are less common in this population.[121] There are significant differences between Chernobyl and Fukushima in terms of radiation doses to the population, making it very difficult to retrospectively estimate internal doses from short-lived radioactive iodine.[122]

Cancer stem cells and radiation resistance: Exposure to ionizing radiation can perturb tissue homeostasis through both induction of cell death/depletion of radiosensitive stem cells resulting in loss of tissue function and genotoxic damage that increases overall cancer risk. The tissues and organs of the body contain populations of cancer

stem cells. These cells are the root cause or seed of cancer origin. These stem cells within the tumor remain dormant for long periods of time. Cells exposed to low-dose radiation acquire resistance to radiation and continue to proliferate to form cancer or differentiate into cancer cells. Cancer radioresistance, or failure of radiotherapy of certain types of tumors, is associated with local invasion, increased metastasis, and poor prognosis. Oral CSCs cause tumor recurrence and metastasis after radiotherapy.[123] There is increasing evidence that CSCs play an important role in post-radiotherapy recurrence and metastasis in many types of cancer. Radiation causes multi-factorial damage to the brain. Neural stem cells are regenerative, reside in specialized neurogenic niches and can generate new neurons.[124] These are different subpopulations within the tumor. These cells are self-renewing and self-differentiating, have a high ability to repair DNA damage, have low levels of reactive oxygen species, and proliferate slowly. These properties make CSCs resistant to various treatments, including radiotherapy. Eradication of all her CSCs is a prerequisite for effective neoplastic therapy, especially resistant glioblastoma tumors, and is therefore of paramount importance to the patient.

Repeated high-dose radiation causes irreversible damage to DNA, impairs signaling, and primarily causes senescence, leading to mitotic catastrophe and loss of cell regenerative capacity. RT prevents cancer cells from growing further.[125] On the other hand, GH-IGF1 signaling, which is involved in the DNA damage response (DDR) and DNA damage repair, determines radio-tolerance of cancer cells. The GH-IGF1 signaling pathway supports radiotherapy and post-radiotherapy cancer repair. Radiation plays an important role in the formation of heterokaryae in Purkinje neurons. The growth hormone-insulin-like growth factor-1 (GH-IGF1) axis plays multiple roles in different systems and supports multiple developmental-inducing effects by promoting cell proliferation and inhibiting apoptosis.[125]

lncRNAs are involved in complex cancer networks and play important roles as oncogenes or tumor suppressor genes in various types of cancer. More specifically, lncRNAs are novel key regulators of cancer progression and metastasis.[126] Silencing the lncRNA CRNDE could reverse CAOV3/R radiotherapy resistance, which could benefit clinical management.[127] ACE inhibitors and ARBs (angiotensin receptor blockers) reduce radiation damage in animal models of lethal gamma rays.

Hematopoietic stem cells are highly sensitive to radiation and are the primary target organ for radiation injury. Short-term exposure to ionizing radiation causes direct and indirect damage to hematopoietic stem cells, leading to acute myelosuppression and long-term hematopoietic injury due to direct and indirect damage to hematopoietic stem cells (HSCs) . HSCs are cells that exhibit DNA damage response (DDR), primarily DNA damage repair, cell cycle arrest, apoptosis, and senescence or the bone marrow (BM) microenvironment. In addition to non-hematopoietic cells, HSC progeny in the BM niche can also regulate HSC fate. Especially in the radiation setting, megakaryocytes can stimulate HSC expansion by either directly secreting cytokines or indirectly promoting osteoblast proliferation.[128]

Use of radiosensitizers: Radiosensitizers are drugs having active substance that helps kill tumor cells upon radiation therapy.[1] Few radiosensitizers such as fluoropyrimidines, gemcitabine, platinum analogues, and fluoropyrimidines are currently used in combination with radiation therapy to enhance its effectiveness. An example of this is the increased sensitivity of tumor cells due to dysregulation of her S-phase cell cycle checkpoint. Gemcitabine proceeds through a similar mechanism to render S-phase cells useless to radiation-induced DNA damage. Platinum analogues such as cisplatin inhibit DNA repair through strand cross-linking, thereby amplifying the effects of radiation-induced DNA damage. Radiation therapy is one of the most effective treatment for patients having laryngeal cancer,[129] rectal, gynaecologic[130] and oesophageal cancer.[131]

Radiation therapy induces immunosuppressive and anti-inflammatory mediators that can confer resistance to radiation. Both immunotherapy and radiotherapy significantly improve cancer survival by controlling metastasis by killing active cancer cells.[131] Immune checkpoint inhibitors (ICIs), tumor vaccines It is also used to protect patients from the harmful effects of radioimmunotherapy such as , adoptive cell therapy and cytokine therapy.[132] Radiotherapy-related risks increase with increasing organ dose.[131] Several cell cycle checkpoint kinases and DNA damage-associated kinases have been engineered to compromise radiotherapy efficacy and target key signaling pathways. is expressed in 2D and 3D cultured cells containing DYRK1A. Moreover, nanomaterials as radiosensitizers show great potential in tumor radiotherapy due to their unique light, heat and electromagnetic effects.[133]

In addition to its direct anticancer cytotoxic effects, ionizing radiation enhances antitumor immune responses by inducing proinflammatory signaling, DNA damage-induced immunogenic cell death, and activation of the innate immune system. can be increased. Innate antitumor immunity may result from the recruitment and stimulation of dendritic cells (DCs), resulting in tumor-specific adaptive T cell priming and immunostimulatory cell infiltration134. Combining therapy with existing therapies such as immune checkpoint inhibitors still poses numerous challenges.[134] There is a need to maximize the immunestimulatory effects of radioimmunotherapy.[135]

CBTH is a strong candidate for wider dissemination and implementation in the cancer population.[136] However, local radiotherapy should be administered to reduce the risk of secondary malignant neoplasms of the gynecological system.[137] In cancer treatment, precision medicine is also given along with radiation therapy. Whole-body precision cancer therapy offers long-term protection. Real-time 3D image-guided radiotherapy IGRT is used to protect nearby tissues from radiation.[138] Patient monitoring and timely diagnosis are critical to improving radiotherapy modalities for cancer.[139]

Conclusion

Radiation therapy is used to save lives in people affected by cancer or cancer cell growth. It is true that radiation destroys cancer cells directly and is used to remove cancerous areas. However, it shows anti-cancer potential, leading to long-term morbidity of cancer cells that is related to the dose and volume of the irradiated organ. It is very unfortunate that there is a global effort to fight the disease, but there is no specific and safe way to treat cancer. Radiation therapy is cheap and out of reach for the poor. Proton therapy optimizes target coverage while reducing dose to non-target structures. The use of protons improves therapeutic efficacy. It is used especially in the treatment of breast cancer. However, there are reports of the use of radiation used in diagnostic procedures and also implicated in cancer vaccination. A number of epigenetic effects of radiation on DNA methylation, histone modifications, and non-coding RNA have been demonstrated. Radiation causes molecular alterations in the genome, adversely affecting cell biology. It is an important carcinogen that also causes neoplastic changes in cells. One of the major challenges associated with radionuclide therapy is non-specific radiation emitted from unbound radioisotopes in normal tissue. One of the major

challenges that need to be resolved is long-term toxicity and efficient removal of radiolabeled substances from the body. Therefore, there is a great need for radiolabeled functional nanomaterials to achieve desirable stability and pharmacokinetics and clearance to minimize radiation exposure in normal tissues. Understanding the cellular processes that determine responses to exposure to ionizing radiation is important for improving radiotherapy and assessing risks to human health after accidental radiation exposure.

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Conflicts of interest

Authors have no conflict of interest.

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