Current Clinical and Medical Education

Received 17 Aug 2024 | Revised 18 Aug 2024 | Accepted 12 Oct 2024 | Published Online 14 Oct 2024

Published By: Vision Publisher

ISSN 2942-0792

CCME 02 (10), 72-91

Functional Nanomaterials for X-Ray Triggered Cancer Therapy: Chemotherapy and Brachytherapy Application Techniques

Noor Al-Huda Raheem Jabbar Abbas †[1], Abbas Mohammed Jassim Nasser [2], Sajjad Sami Rahman Hussein [3], Hiba Maani Aboud Muheisen [4]

[1,2] The University of Wasit, College of Sciences, Medical Physics Department, Iraq

[3]The University of Misan, College of Sciences, Chemistry Department, Iraq

[4]The University of Wasit, College of Sciences, Chemistry Department, Iraq

Abstracts: One of the most used cancer therapies, radiation therapy (RT), and a relatively new one, radio-dynamic therapy (RDT), both make use of X-rays, a type of ionising radiation that has a high intensity and strong tissue-penetration. Unsatisfactory treatment efficacy and substantial harm to healthy tissues can result from X-rays' nonspecific absorption and the unique tumour microenvironment. The rapid advancement of nanotechnology has opened up numerous possibilities for the creation of useful nanoparticles and approaches to address these issues. We will review the current state of functional nanomaterials and related strategies, talk about how they overcome obstacles to make RT and RDT safer and more effective, and then comment on the difficulties and potential solutions for nanomedicine-based efficient X-ray-triggered cancer therapy. Radiation therapy has been helpful for cancer patients for more than 100 years. Modern, highly-technological treatment methods make it feasible to customise radiation doses such that normal tissues around the cancer receive the least amount of radiation possible. Despite tremendous scientific progress over the past few decades, there are still some cancers where we are fighting to improve patient survival rates. The urgent requirement for additional advances, including those utilising nanotechnology, is emphasised by this. Various treatment objectives may be advanced with the use of radiation. It could, for instance, make surgery more successful, slow the spread of cancer, or alleviate symptoms of advanced cancer. A photon beam is the most common kind of radiation therapy instrument. Although X-rays use lesser doses of photons, they are nevertheless utilised. Localised tumours can be targeted by photon beams. Radiation is scattered as photon beams travel through the body. Even after they've reached the tumour, these rays go on to normal tissue. A form of cancer treatment known as radiation therapy involves the use of high-energy particles or waves, such as X-rays, gamma rays, electron beams, or another form of energy, to inhibit the development and division of cancer cells. Consequently, the cell will progressively contract and eventually die. While radiation therapy does its best to kill cancer cells while sparing healthy cells, it can occasionally harm healthy cells nearby the cancer or prevent them from dividing and expanding by damaging their DNA. Following surgery to remove the cancerous tumour, radiotherapy may be administered as part of the treatment plan to reduce the likelihood of tumour recurrence. Before, after, or in conjunction with chemotherapy, radiation treatment is administered to tumours that are particularly vulnerable in order to maximise the efficacy of the drug.

Keyword:X-Ray, Cancer Therapy: Brachytherapy, Techniques, Radiation Therapy

Corresponding Author: Ali Layth Hanoon ,Engineering Medical Devices, Al-Esraa University, Iraq.

Introduction

The extraordinary penetrating depth and powerful energy of X-rays have piqued the curiosity of many researchers since their discovery in 1895 by Wilhelm Wilhelm Roentgen. Attenuation of energy and generation of electrons and photons would result from X-ray contact with matter. There has been a lot of research into the particular physical processes of X-rays as they interact with atoms over the past hundred years: In contrast to the elastic Rayleigh scattering, the inelastic Compton scattering of X-rays would transfer some of the incident proton's energy to an ejected electron [1, 2]. The photoelectric effect of X-rays would also cause electron ejection and the generation of excess energy, which would be released as Auger electrons (short-range secondary electrons) or fluorescent photons. The aforementioned process has increased X-ray's use in many domains, including the biomedical treatment of diseases. Cancer ranks high among the most dangerous diseases to human health on a global scale. One use of contrast chemicals in X-ray computed tomography (CT) for tumour diagnosis is the acquisition of three-dimensional information about the human body through differential X-ray attenuation (or absorption) [3, 4]. One of the most common approaches to treating cancer in clinical settings is X-ray initiated radiation therapy, often known as radiotherapy (RT). In RT, X-ray emissive photoelectrons and Compton electrons can damage DNA directly, and Auger electrons can destroy DNA and other cellular components indirectly by reacting with the water around them to produce reactive oxygen species (ROS) [5]. This would induce cellular apoptosis and necrosis, which would inhibit tumour growth. Despite RT's extensive use in treating over 50% of cancer patients, there are still some drawbacks to this treatment modality. These include tumour hypoxia-related RT resistance, severe side effects on normal tissues from high-dose radiation, compromised therapeutic effect from insufficient X-ray absorption of tumours, and the inability to treat cancer cells that have spread to other parts of the body. Imaging with X-ray excited optical luminescence (XEOL) and cancer treatment using X-ray induced photodynamic therapy (also known as radiodynamic therapy, RDT) have both been investigated as of late. The photodynamic impact of photosensitisers is typically used in RDT to initiate ROS production, which in turn kills cancer cells [8,9]. Benefiting from both practical clinical facilities and a high penetration-depth, RDT is an improvement over traditional photodynamic therapy. Alternatively, compared to RT treatment, RDT is better since it uses a much lower amount of X-ray irradiation. Nevertheless, RDT is still in its early stages and could benefit from additional research into multifunctional agents and specific mechanisms to broaden its scope of use [6]. Many people are interested in using different functional nanomaterials to enhance the therapeutic outcome of cancer treatments, which has been sparked by the development of nanomedicine [10,11]. Nanomaterials are able to circulate through the blood and be passively or actively targeted to accumulate in tumours due to their nanoscale size. Conversely, new approaches to improving therapeutic effects can be facilitated by investigating nanomaterials with tailorable physiochemical characteristics. In order to improve the efficacy of X-ray triggered cancer therapy, new nanomedicine technologies utilising a variety of functional nanomaterials have been developed in recent years. In this article, we will go over the role that nanomaterials play in improving X-ray triggered cancer treatment and review the latest developments in RT and RDT. New approaches to radiation therapy that incorporate nanomaterials will be reviewed and classified. Furthermore, we will go over the various nanomaterials used in RDT along with the processes that go along with them.

Nearly 41% of American babies born today will be diagnosed with cancer at some point in their lifetime. This amounts to 1,500,000 new cancer diagnoses in the United States in the past year. Despite the ongoing advancements in

cancer therapy science and technology, there is still much to be accomplished [7]. Although it varies substantially by illness type, the overall 5-year survival rate for cancer patients is significantly lower than that of the general population, at 65%. Roughly 600,000 Americans lost their lives to cancer in 2010. New and improved methods of cancer prevention and treatment are, therefore, clearly, urgently required. This volume details several uses of radiation oncology based on nanotechnology, all with the common goal of improving patient outcomes. This introductory chapter aims primarily to provide a snapshot of cancer radiation therapy.

On order to identify the organs that would be subjected to radiation, physicians captured images at an angle parallel to the therapy beams. The use of either generic or custom-made radio-opaque blocks allowed them to safeguard these organs. About this time, Hounsfield invented computed tomography [8]. However, regular CT-based treatment planning couldn't happen until the 1990s, when computers and related networks acquired a certain degree of sophistication. Supplementing computed tomography (CT) scans with additional imaging modalities, such as positron emission tomography (PET) and magnetic resonance imaging (MRI), is a standard procedure for better tumour volume definition.

Using the MV x-rays from the treatment unit, beams-eye view images of the treatment field could be captured on radiographic film for quite some time. For the most part, film is no longer used in electronic portal imaging systems. Modern LINACs also feature detectors and kV x-ray tubes attached to the gantry, which give superior pictures for getting the patient ready. This setup can also take the CT photographs that are now routinely taken in many clinics to make sure the patients are positioned correctly. Radiation can be delivered to patients through multiple methods, not limited to external beams alone. Greek for "short distance," [9-11] brachytherapy is an alternative approach that uses sealed radioactive sources inserted into or applied directly to the tumour. While radium was initially the material of choice for most brachytherapy treatments, the discovery of artificial radioactivity in 1934 opened the door to a plethora of new options, including as Ir-192, Au-198, and I-125. Nanotechnology has the ability to improve the efficacy of brachytherapy treatments in addition to external beam radiotherapy, which is the primary focus of this effort because of its field-wide ubiquity.

Current status, medication prospects, and cancer treatment and beyond

Millions of lives are lost annually due to cancer, an aberrant cellular condition characterised by unchecked cell proliferation and the development of aggressive malignancies. Our knowledge about the disease is expanding at a rapid pace, thanks to new insights into the molecular mechanisms of disease progression. As a result, numerous novel therapy regimens have been developed and are undergoing trials. A wide variety of malignancies are now being treated with various combinations of medicines that have been developed in recent decades. Not long ago, targeted drug therapy, immunotherapy, and customised medications were not widely used [12-15]. As more and more cancer-specific biomarkers are discovered and as more and more cancer kinds receive systematic therapy, the area of cancer research and treatment is advancing rapidly, leading to longer disease-free survival times for patients. Chemotherapy is still a popular choice for cancer treatment, even though it has serious negative consequences on patients' physical and mental health, and there is mounting evidence that more targeted and systematic approaches may be the way of the future.

After hearing that mustard gas may kill bone marrow and lymphatic tissues, the concept of chemotherapy—which involves using harmful chemicals and medications to eradicate malignant cells—was born. Nitrogen mustard, a gas derivative, was then used to confirm the effects in mice by causing lymphoma tissues to regress. The initial patient to get this nitrogen mustard was a 48-year-old woman with lymphosarcoma, whose malignancy initially shrank and disappeared after treatment [16, 17]. Though he succumbed to his illness after a relapse, the clandestine military experiment at Yale University set the stage for the use of chemicals in cancer treatment and the evolution of cancer chemotherapy as a field. To a large extent, chemotherapy is effective because it prevents the cancer cells from dividing and growing. In addition to experiencing extremely high levels of endogenous stress, cancer cells typically divide and expand at a far faster rate than normal cells. They are thus easier targets for the medications, which can kill them faster than other cells in the vicinity. The following inhibitor therapies have shown promise in the treatment of solid cancers: inhibitors of polyadenosine diphosphate-ribose polymerase (PARP), angiogenesis inhibitors, histone deacetylase (HDAC) inhibitors, p53/mouse double minute 2 homolog (MDM2) inhibitors, inhibitors of the hedgehog pathway, tyrosine kinase inhibitors, and proteasome inhibitors. There are various forms of chemotherapy, each with the potential to influence target cells in its own unique way [18, 19]. It is possible that some of the treatments will have an effect on the quality of proteins within cells, making them inactive and therefore influencing important physiological circuits within cells. Such compounds include proteasome inhibitors, autophagy suppressors, and major chaperone repressors. Various medications have the potential to affect the body's metabolic rate by focussing on specific hormones.

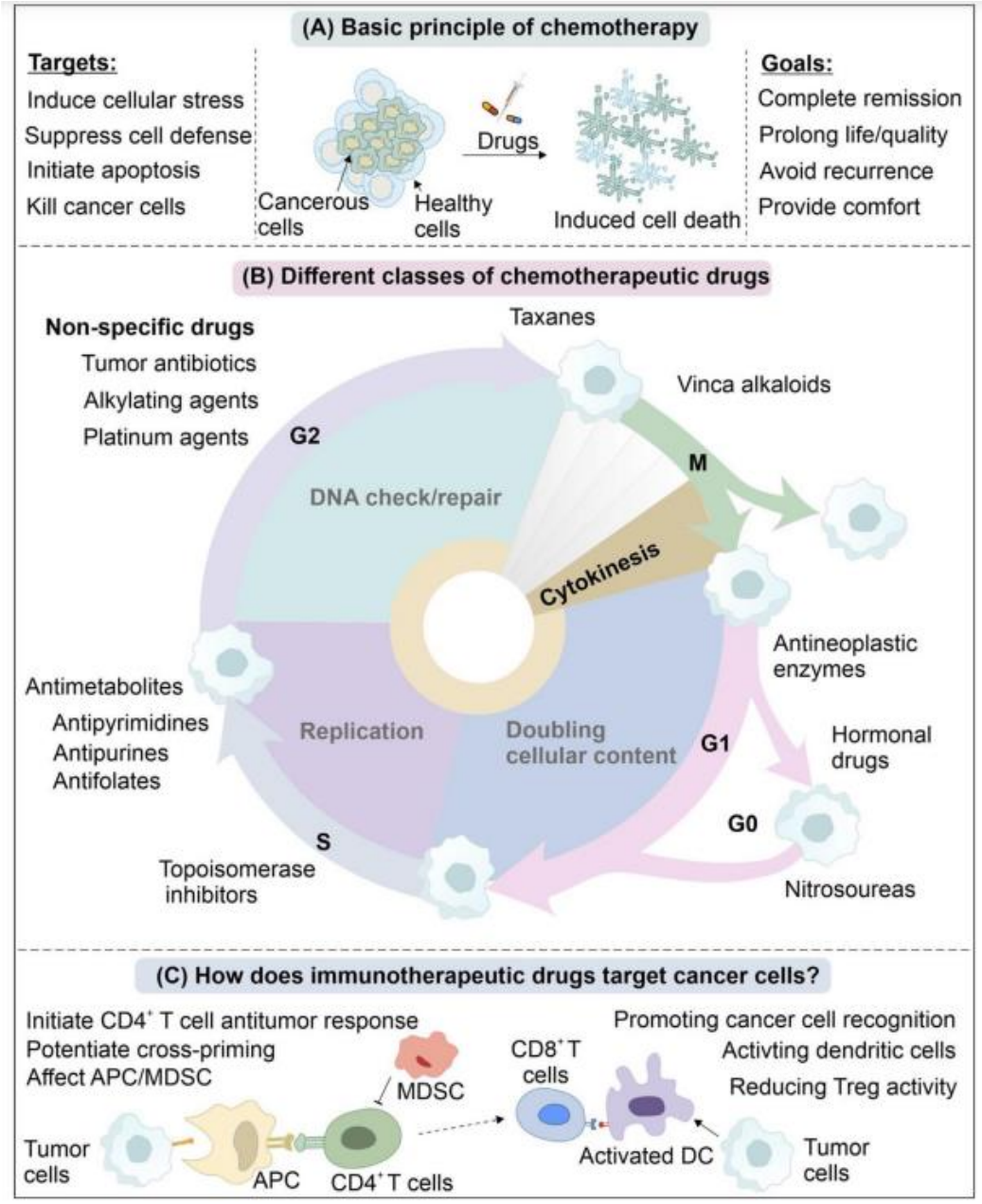

Figure 1. (A) Chemotherapy fundamentals, (B) several chemotherapeutic drug classes, and (C) immunotherapy methods for destroying cancer cells.

Radiosensitizing nanomaterials

Nanomaterials having a high atomic number (Z) could serve as effective radiosensitizers, enhancing the effectiveness of a given radiation dose, due to the positive correlation between the photoelectric effect of X-ray radiation and (Z/E)3. For local enhancement of radiation deposition at the tumour site, the most studied radiosensitizers are highly chemically inert gold nanostructures (Z=79). It should be mentioned that high-Z elements have a great X-ray attenuation ability, hence CT imaging using the same nanomaterials is commonly used to identify tumours before RT therapy. There is evidence that many additional nanomaterials containing high-Z elements can be used for RT treatment by utilising their great photoelectric absorption capabilities [20-23]. One example is the use of upconversion nanoparticles, which concentrate a larger dose in a targeted area, allowing for more effective radiosensitization. Optimal treatment window selection is facilitated by the timely tracking of their biodistribution by CT, MR, or

upconversion fluorescence imaging. Using poly(vinylpyrrolidone) (PVP) as a radiosensitizer, Zhang et al. created Bi2Se3 nanoplates, taking into account that bismuth has the greatest atomic number (Z=83) among nonradiative elements and selenide possesses anticancer action. Research has shown that Bi2Se3 nanoplates can aggregate inside tumours, effectively halt tumour growth in response to ionising radiation, and then be removed by oxygenation after 90 days. Additional research on nanosensitizer toxicity, biodistribution, and clearance behaviour has been stimulated by this work. Shen et al. recently developed a chelator-free method for labelling 64Cu into a renal-clearable nano radiosensitizer by coordinating tungsten ions (WVI) with gallic acid (GA). The accumulation of W-GA nanodots in the tumour, as observed using positron emission tomography (PET) imaging, could significantly enhance the RT efficacy in preventing tumour growth [24-27]. The fast excretion of W-GA nanodots following treatment eliminates worries about heavy metal toxicity in the long run and bodes well for their potential use in therapeutic settings. While traditional nanoparticles containing high-Z elements can improve tumour X-ray deposition, other nanoparticles with unique chemical characteristics have evolved as radiosensitizers that work in different ways. In vitro studies have shown that RT may be more effective in killing cancer cells when exposed to silver ions produced by Ag nanostructures. Furthermore, it has been noted that iron-based nanomaterials can enhance the generation of reactive oxygen species (ROS) when exposed to X-rays, thanks to the iron-catalyzed Haber-Weiss cycle and Fenton reaction [28-30]. In addition, Bu et al. found that X-ray irradiation for cancer cells may be enhanced by rearranging the cell cycle to the radiosensitive G2/M phase and downregulating proteins related to DNA repair through the continuous Fenton reaction induced by iron ions in nanomaterials.

Tuning the Transmembrane Environment with Nanomaterials

A distinct tumour microenvironment (TME) defined by low oxygen levels (hypoxia), an acidic pH (acidosis), and an elevated concentration of hydrogen peroxide would emerge from a tumor's fast development and disorganised blood arteries. Oxygen is crucial during radiation treatment because it inhibits the ability of cells to repair DNA damages caused by radiation. Radiation resistance, which in turn causes unsatisfactory DNA damage and treatment failure, is thus partially caused by oxygen shortage in solid tumours. In addition, both tumoral hypoxia and radiation therapy would lead to an increase in hypoxia inducible factor 1 (HIF1) activity, which could shield tumour and endothelial cells from cytotoxic therapeutic damage while decreasing the effectiveness of radiation therapy. To optimise RT cancer treatment, several nanotechnology-based therapeutic strategies have been suggested to modify the TME [31, 32]. These strategies include oxygen supply, oxygen generation, GSH concentration modulation, and an oxygen-independent therapy strategy. Nanocarriers for oxygen transport were created to alleviate tumour hypoxia and improve the effectiveness of radiation therapy (RT), in addition to the aforementioned way of hypoxia alleviation by hyperthermia in combination therapy. The great oxygen solubility of perfluorocarbons (PFCs) has led to their extensive use as a synthetic blood substitute. In order to stabilise PFC on a nanoscale and prolong blood circulation, some groups have used polymer, erythrocyte membrane, human serum albumin, or hollow inorganic nanomaterials. This has been successful in relieving hypoxia in tumours and improving RT [33-35]. Combining the RT sensitisation by high-Z elements with the oxygen transport capabilities of PFC, one example is hollow Bi2Se3 nanoparticles loaded with PFC, also known as Bi2Se3@PFC. In addition, the radio-sensitization effect may be enhanced synergistically by externally triggering the burst release of oxygen from Bi2Se3@PFC using near-infrared laser irradiation.

X-Ray Radiation

While certain materials do not change the amount of x-rays that can flow through them, others absorb or scatter them, making them less powerful. The relationship between the fractional number of photons attenuated by an infinitesimally thin slab of material and its thickness, denoted as μ, is direct. This coefficient incorporates the separate absorption and scattering effect coefficients [36, 37]. We give a short overview of them in the following paragraphs since they are relevant to radiation-nanoparticle interactions. Regular distribution. No energy is lost when x-rays are dispersed in a coherent pattern. Electrons in an atom are vibrated by an electromagnetic wave, which causes them to emit radiation with the same wavelength. When the released waves combine, it produces the scattered x-ray. Because of the minimal likelihood of this interaction between high-energy photons and soft tissue and the absence of energy deposition in the medium, it does not have any bearing on radiation treatment [38, 39]. It lowers image quality in diagnostic imaging by adding to patient scatter.

The photoelectric effect is a real thing. Photoelectric interactions occur when light rays interact with electrons embedded in a substance. The kinetic energy of the ejected electron is equal to the energy difference between the incident photon and the bound energy of the atom, which is caused by the contact, and the electron is ejected from the atom. An approximate formula for the mass attenuation coefficient of photoelectric absorption is Z3/E3, where Z is the atomic number of the medium and E is the photon energy. This interaction is frequently seen in soft tissue with low-energy incident photons (<0.03 MeV), but it is extremely unusual when using the megavoltage energies used in external beam radiation therapy. Diagnostic x-ray images of bones, which have a high Z, display a great deal of contrast due to the fact that the photoelectric effect is Z dependant.

One potential application of this dependence to improve the therapeutic effect of radiation is the use of gold nanoparticles, which will be covered in subsequent chapters. An increase in x-ray absorption and photoelectric effect electron release can be achieved by adding gold nanoparticles, as the atomic number of gold is more than ten times higher than that of soft tissue [40-43]. Connections between Compton waves. In x-ray interactions with soft tissue, Compton interactions are more common at lower x-ray energies, while the photoelectric effect takes centre stage at higher x-ray energies. Interactions between the x-ray photon and electrons involve rather loose bindings. In every interaction, part of the energy is lost through scattering and part is gained by the electron, which is then liberated from the atom. As photon energy increases, the likelihood of a Compton interaction decreases. Since these interactions include loosely bound electrons, the interaction probability is mostly influenced by electron density and is practically independent of atomic number. This suggests that the presence of bone in the beam's path does not substantially alter the radiation dose to tissues downstream of it [44-47]. Assembling matching sets. In x-ray absorption, a pair is formed. An x-ray photon undergoes this transformation when it approaches the nucleus of an atom and becomes a positron-electron pair, which imparts mass. The incident x-ray must have a minimum energy of 1.02 MeV, the mass equivalent of this pair (2 × 0.51 MeV), in order for this interaction to occur. At this point, the two particles share equally any energy that exceeds it.

Advantages of Photon Beam Cancer Treatment

The dosage is depth dependent. The shape of the change in deposited dosage with depth in a material is considerably different from the x-ray beam attenuation, which follows a form that combines exponential attenuation and 1/r2 fall-off with increasing source distance. Photons deposit their energy in the form of high-energy electrons that settle

downstream after interacting with tissues on the patient's surface. An initial dose increase in the accumulation zone is followed by a maximum as the number of electrons implicated increases at deeper and deeper depths. The "skin-sparing effect" describes this phenomenon, which occurs when deeper tissues receive a little larger dosage than the skin, which is more sensitive. Photon flux decreases with depth due to attenuation and the 1/r2 fall-off. So, as one goes deeper, the dosage drops because the density of the electrons that deposit it drops with depth. Dosage administration [48, 49]. The structure of the dose distribution can be described using isodose curves, which are lines that link places that receive the same dose. Dose uniformity is usually observed across the centre of a broad beam. Although beam modifiers can change the highly non-uniform dose distributions of some modern LINACs—which will be discussed later on—a uniform distribution is still required for these machines [50]. The shape of the dosage distribution outside and at the beam's borders is determined by geometric penumbra, collimation, and beam energy, which is the degree of forward photon dispersion. The geometric penumbra is caused by the fact that the LINAC's focal spot is limited in size.

Use of Electron Beams in Therapeutic Procedures

As indicated before, photoelectric, Compton, or pair creation processes set the electrons in the medium in motion. It is actually electrons, not photons that deposit the radiation dose. Current LINACS have the potential to produce electron energies ranging from 4 to 20 MeV, or even higher, making them another potential electron source. The energy of the electrons gradually decreases as they pass through the medium, regardless of their initial source, until they are captured by atoms. The collision of electrons in inelastic atoms. The energy loss rate as a result of atomic electron cloud excitation or ionisation is usually lower in higher-Z materials because the density of bound electrons is a feature that is reliant on electron density. For high-energy electrons ($E > 1$ MeV), the energy loss rate through water (or soft tissue) is 2 MeV/cm, which is rather constant. This allows us to determine the maximum depth to which electron beams can penetrate; for example, when irradiating a node in the neck with an 8-MeV beam, the spinal cord will only get a fraction of the dosage if we penetrate at least 4 cm. The impact of atomic nuclei is inelastic. Electrons lose energy via Bremsstrahlung x-rays as they approach nuclei because the nucleus's Coulombic force deflects and slows them down. For an electron with a higher kinetic energy and a larger Z, the likelihood of a bremsstrahlung contact grows [51]. Diagnostic x-ray tubes and linear accelerators generate high-energy photon beams when high-energy electrons collide with their respective objects. Repetitive Coulomb scatterings twist high-energy photo- and Compton electrons as they move through tissue. As a function of both electron energy and Z2, the scattering cross section has an inverse relationship.

Cancer Treatment Using Radioactive Agents

Deterioration of Alpha

When a nucleus decays, it releases a single alpha particle, which increases its stability. Two protons and two neutrons make up a helium nucleus. This disintegration can only occur in very large nuclei. Its half-life is 1622 years, and it decays from Ra-226 to Rn-222, making it a useful therapeutic agent for a long time. Radon emits a flurry of gamma rays as it decays into stable lead. These photons were used to deliver doses in cancer treatments.

A Brief Overview of Beta Decay

A beta particle, an electron released from a nucleus, can be either positively or negatively charged during beta decay. A nuclear nucleus can increase its atomic number through nuclear nucleus transmutation if its neutron/proton ratio is excessively high. An electron is released into the atmosphere all at once. [52, 53] There is a continuous energy spectrum that releases beta particles up to an energy unique to decay. A nucleus may undergo decomposition and release a positive electron (positron) if its neutron-to-proton ratio falls below the stability threshold. A metabolically active chemical, like F-18, is linked to a positron-emitting isotope for use in PET scans. The rapid interaction of the isotope's positrons with electrons in tissue annihilates both the positron and the electron, releasing two 511 keV photons, one of which is moving in the opposite direction. By detecting these photons, it is able to reconstruct the distribution of the metabolically active molecule.

Techniques for radiation therapy

Cancer cells can be killed by radiation, a physical agent. Ionising radiation gets its name from the fact that it creates ions—particles with electric charges—that deposit energy into the cells of the tissues it passes through. It is possible to use this stored energy to destroy cancer cells, or to make genetic changes that cause cancer cells to die. When exposed to high-energy radiation, cells are unable to divide and reproduce because the DNA, the cell's genetic material, is damaged. Radiation can damage both healthy and diseased cells; nevertheless, the goal of radiation therapy is to destroy cancer cells while exposing healthy cells to the smallest feasible amount, either directly or indirectly. In most cases, normal cells have a higher capacity for self-repair and maintenance of normal function condition compared to cancer cells. Because cancer cells aren't as good at healing damage from radiation as normal cells, a process called differential cancer cell death happens. Cancer patients looking for symptom relief have options when it comes to radiation treatments: curative and palliative. Another reason radiation therapy could be used is as a combination strategy with other forms of treatment including immunotherapy, surgery [54-57], or chemotherapy. Preoperative radiation treatment, also known as neoadjuvant therapy, aims to shrink tumours before surgery. After surgery, radiation can be used as adjuvant therapy to kill any leftover tumour cells, no matter how tiny. It is well-known that some tumour types respond differently to radiation treatment than others. There are two ways to direct radiation beams directly at malignancies. External beam radiation involves bringing high-energy rays (photons, protons, or particle radiation) into the body and directing them onto the tumor's location. Here, this is considered the gold standard in healthcare. Radioactive sources, either in the form of seeds or catheters, are inserted directly into the tumour site during brachytherapy, also called internal radiation. Regularly treating gynaecological and prostate malignancies, or when retreatment is required, is when this is most typically utilised because of its short-lived effects.

Fractionation

The radiobiological properties of cancerous and noncancerous tissues are distinct, necessitating a fractionated radiation treatment regimen. Generally speaking, these regimens boost normal tissues' survival advantage over cancer cells, as normal cells are superior at repairing radiation damage below the lethal threshold. Normal cells have more time to repair damage before replicating since their division rate is slower compared to cancer cells. A number of regimens that compared different treatment plans based on total dose, fraction number, and total treatment time were developed from early 1920s investigations on the effects of fractionated radiation therapy. Present regimes are based

on the linear-quadratic formula, which accounts for the time-dose variables for various tumour forms and healthy tissues.

3-D Conformal Radiation Therapy (3DCRT)

2D radiation therapy using rectangular fields based on plain X-ray imaging has been substantially replaced by 3D radiation therapy based on CT imaging. This new method allows for optimal beam placement and shielding by precisely identifying the cancer and essential normal organ structures. The objective of radiation therapy is to treat the entire tumour volume, which includes the gross tumour volume (GTV), the margin for microscopic tumour extension (CTV), and an extra margin for complications related to organ movements and changes in setup (PTV).

Specifically calibrated radiation therapy

The oncologist can customise radiation dosages to the tumor's specific structure utilising IMRT, avoiding crucial organs in the process. IMRT primarily consists of two parts: inverse planning software and computer-controlled intensity-modulation of several radiation beams throughout the treatment. Many therapy departments now have access to IMRT thanks to tomotherapy technology and linear accelerators with static or dynamic multi-leaf collimators. This has led to an improvement in the treatment ratio for several tumour locales, including gynaecological, prostate, and head and neck cancers. Radiation treatment using imaging guidance (IGRT) As treatment margins become more conformal and narrow, the chance of missing a tumour due to changes in patient positioning or the movement of organs grows. Unwanted radiation exposure to healthy organs can occur with even a slight misalignment if critical tissues are situated close to the tumour [58, 59]. It is possible to detect and fix these errors with the help of IGRT, which makes use of data acquired during pre-radiotherapy imaging. Greater accuracy has allowed for dose escalation, which has improved the therapeutic ratio for several tumour sites, including as prostate and head and neck malignancies.

"Stomatographic body radiation therapy" is the acronym for this method.

Recent technological advancements have made SBRT a viable option for targeting small, well-defined primary and oligometastatic cancers throughout the body. This is achieved by accurately administering very high radiation doses to each patient within a relatively short period of treatment fractions. The large dose can potentially harm any neighbouring healthy tissue. On the other hand, the low and unremarkable fraction of normal tissue in the high dosage zone means that no harm of clinical relevance occurs. When it comes to treating early stage non-small cell lung cancer in patients who aren't surgical candidates, SBRT has proven extraordinary success. Spinal cord, pancreatic, oligometastasis, liver, kidney, head/neck, and prostate cancers are among the many more forms of tumours.

When it comes to radiation therapy for cancer, photon radiation (including x-rays and gamma rays) is commonly used.

The radiation charge of a photon beam is almost nonexistent, and it is incredibly light. Radiation therapy frequently uses photons like X-rays and gamma rays to treat various forms of cancer. Electromagnetic radiations that are sparsely ionising, like gamma and X-rays, are made up of energy particles called photons. Cathode ray tubes and linear accelerators generate X-rays and gamma rays, respectively, from the breakdown of radioactive materials like caesium, cobalt-60, and radium.

Classification and Features of Cell Death

Similar to other anticancer treatments, radiation therapy destroys cancer cells by inducing multiple types of cell death. Radiation treatment to eradicate cancer cells is a time-consuming process. Radiation treatment takes several hours, days, or weeks before it causes cancer cells to die. A number of weeks or months after radiation treatment ends, cancer cells will still be dying off. Radiotherapy is one cancer treatment modality that makes advantage of programmed cell death, often known as apoptosis. The process of cell death is characterised by the demise of cells and the formation of apoptotic bodies. Mitochondria play a crucial role in programmed cell demise. Common causes of cellular blebbing include nuclear margination, DNA fragmentation, and compressed chromatin. The cell membranes of apoptotic cells are usually left intact. Inducing cell death in cancer cells is a critical component of radiation therapy's efficacy. Mitotic catastrophes occur when cells die either during or after aberrant cell division, which is known as mitosis. Massive cells with aberrant nuclear morphology (many nuclei) result from chromosome mis-segregation. Cells frequently include micronuclei and centrosomes that have been duplicated. The great bulk of cell death in solid tumours after irradiation is caused by abnormal mitotic processes. Both of these mechanisms are major ways in which ionising radiation kills cells. The process of necrosis causes cells to expand substantially due to the breakdown of their membranes. Atypical nuclear shape is characterised by vacuolization, non-condensed chromatin, and disintegrating cellular organelles; this is followed by mitochondrial expansion and plasma membrane rupture, both of which lead to the loss of intracellular contents. Necrosis caused by radiation is uncommon, however it has been observed in cancer cell lines and tissues.

Cells become senile when they lose their ability to divide and replicate with the passage of time. Even though they stop dividing and producing new DNA, senescent cells eventually flatten out and enlarge, but they are still functioning. They get even more fine-grained as well. Cancer cells supposedly go through senescence and die largely by apoptosis after radiation treatment damages DNA and produces other types of cellular stress. The mechanism of autophagy has very now been elucidated. This form of cancer cell death is brought about by radiation. Autophagy, a form of programmed cell death regulated by genes, involves the autophagic/lysosomal compartment. Creating double-membrane vacuoles in the cytoplasm defines it, which sequesters organelles like ribosomes and condensed nuclear chromatin. There are various types of radiation-induced cell death, each involving a unique combination of genes and intracellular mechanisms. While the p53-Caspases-Cytochrome c cascade is associated with mitotic catastrophe, the ATM-p53-Bax-Cytochrome c-Caspases pathway has been associated with apoptosis. The TNF (alpha) -PARP-JNK-Caspases route and the MYC-INK4A-ARF-p53-p21 pathway are two of the many mechanisms that contribute to senescence. The PI3K-Akt-mTOR cascade is thought to have a major impact on autophagy. While most of the processes involved in carcinogenesis and radiation resistance are interrelated, there is still much that is unknown regarding the cell death pathways that lead cancer cells to resist radiation treatment. However, it is still not known how radiation causes the many types of cancer cell death to occur. In recent years, our knowledge of the several metabolic pathways that govern cell death after radiation exposure has been rapidly expanding.

Using radiation therapy to treat cancer

The primary goal of radiation therapy for cancer is cell death. This is achieved by damaging deoxyribonucleic acid (DNA) and other important biological components. Radiation only causes around one-third of the biological harm

when it interacts directly with these molecules. Because of their great reactivity, free radicals can damage or even kill biological molecules; they are produced when water is excited or ionised by radiation and are mostly to blame for the damage [60]. More than two-thirds of the biological damage caused by x-rays occurs as a result of the second effect, another name for indirect action. Importantly, chemical protectors or sensitisers can change indirect action.

Cellular radiation sensitivity is characterised by four basic pathways.

Step one: fix it

Radiation can cause four basic forms of DNA damage: protein crosslinks, base alterations, single-strand breaks, and double-strand breaks. The most serious problem is with double-strand breaks because they mend so slowly. The rest, like DNA protein cross-links, are either very infrequent or easily fixed, like single-strand breaks and nucleotide alterations. Each of the four pathways can play a role in radiation carcinogenesis, which is an independent but interrelated process.

Bringing More:

In time, the population lost to irradiation can be replaced by the proliferation of certain types of undamaged cells. It would be fantastic if this process could occur more rapidly in healthy tissues, such as during healing.

Changing Budgets

Due to the fact that some phases of the cell cycle are more resistant to radiation than others, after irradiation a larger percentage of cells will be in the radiation-resistant phase. This means that subsequent irradiation won't be as efficient in killing cancer cells. Scheduling the next treatments in such a way that the cohort's tumour cells return to a sensitive phase while the healthy cells do not would be ideal.

Reoxygenation

Cells that are hypoxic, or oxygen-starved, are unaffected by radiation. How much of a substance needs to be present in an oxygenated environment compared to a hypoxic one is the oxygen enhancement ratio (OER). This is dependent on both the radiation type (described below) and the cell cycle phase. The tumor's core cells may be hypoxic and therapy resistant due to the limited diffusion of oxygen in tissues. By exposing hypoxic regions to oxygen and distributing the radiation over several fractions, it is feasible to eliminate the outer parts of the tumour by making them more susceptible to radiation. Depending on the kind of tissue, the relative importance and effectiveness of these processes can change substantially. Cells that divide rapidly, like skin cells or intestinal lining, are more vulnerable to irradiation than slower-dividing cells, such neurones.

Putting Healthy Tissues at Risk

As previously indicated, determining the dosage to provide to the tumour involves taking into account the possibility for damage to healthy tissues. Two distinct forms of harm can manifest: acute and late. Rapidly dividing tissues are more vulnerable to damage in the short term. Because radiation kills cells during mitosis, the rate of cell death is highest in rapidly dividing cells. For instance, the oropharynx, oesophagus, and rectum all have skin and mucosal surfaces. Head and neck cancer treatments often cause mucositis, a side effect that often becomes worse around the third or fourth week of treatment.

Normal proliferation of mucosal cells in response to cell death normally causes it to calm down after that. Because stopping treatment abruptly reduces tumour control and lengthens treatment duration, clinical staff aim to minimise adverse responses. Once the first few weeks of treatment are finished, mucositis usually disappears on its own. The effects of irradiation don't become apparent for at least six months, and often for years after the fact. Esophageal stricture, pulmonary fibrosis, and various other forms of organ damage are among these consequences. While in certain situations (such as oesophagitis) there are clear acute symptoms, in others (such as heart damage) there are no such symptoms but the late repercussions are already known.

Radiation therapy increases the risk of developing secondary cancers. The severity of cancer induction is considered a stochastic impact, and it worsens with dosage, in contrast to the previously listed harmful consequences. So, while the chance of incidence increases with dosage, the severity remains constant. Secondary malignancies caused by radiation can develop years after radiation treatment for childhood cancers like Hodgkin's lymphoma or retinoblastoma [60, 61]. The risks of the current cancer much exceed those of a possible future cancer, thus clinicians are not going to skip therapy for a patient because they are afraid of secondary cancers. Frequently, the prospect of secondary malignancies is raised when contrasting treatment modalities that appear to have comparable tumour control outcomes, like proton treatments and IMRT. This is why research and development efforts aimed at improving treatment techniques that reduce dose to non-target tissues are being prioritised.

Imaging-Guided Radiation Therapy for Treatment

Before radiation therapy, patients would arrange their tattoos so that the lasers in the treatment chamber were parallel to each other. Daily uncertainty in patient posture can be relatively large due to the skin's pliability. Accurate therapy administration has led to a growth in the requirement for more constant and precise patient placement. The use of x-ray imaging to determine the optimal position of patients during surgical procedures was the norm for quite some time. The first step was electronic portal imaging, which created images using the radiation from the LINAC. Since these images are created using high energy photons (MV), which are mostly influenced by Compton interactions, there is less inherent contrast in them when contrasted with low energy x-rays. Still, for most patients, they are enough for alignment. To circumvent this issue, more recent LINAC systems equip the gantry with kV x-ray tubes and detectors on arms. With this setup, we can acquire higher-quality x-rays of the patient while they are positioned for treatment. By comparing daily x-ray scans with treatment plan photos, therapists can fine-tune the couch position before therapy begins. One big advantage of this imaging technique is the high-quality pictures it produces. However, it is still only planar imaging, which is great for bones but sometimes misses cancers and other soft tissues. In a case where the cancer is truly associated with bone, patient alignment according to bone is a reasonable approach; nevertheless, the tumor's mobility in relation to the bony landmarks is yet unknown. Instead of utilising skin marks, this works better. As with other cancers of the abdomen and chest, this is the case with prostate cancer. To get around this, a CT scan can be obtained by either introducing radio-opaque markers into the tumour or by moving the kV x-ray tube and detector throughout the body. The second approach, which is known as cone-beam CT because of its geometric design, generates CT images that are not of diagnostic imaging quality but are usually sufficient for identifying and visualising soft tissue targets.

Brachytherapy is a form of medicine

Brachytherapy involves directly introducing radioactive sources into or onto the tumour using sealed containers. Normal tissues nearby or far away receive low doses because the high dose to the source rapidly decreases with distance (1/r2).

Methods for the Application of Brachytherapy

Depending on the tumor's size and location, one of several typical brachytherapy sources can be utilised to treat tumours.

1.Brachytherapy administered between the interstitial spaces.

The process involves inserting radioactive sources into the tissue itself. Both permanent and temporary sources are used; the former is used when I-125 seeds are implanted in the prostate, and the latter is withdrawn when the necessary dose has been administered. A permanent implant only requires surgery once, which is a major benefit. On the other hand, a temporary implant could provide more flexibility and control over the distribution of both the source and the dose. Typically, a temporary implant will begin with the insertion of a catheter or catheters into the tissues. After that, dummy sources are placed into the catheters and the dose distribution is determined by taking x-ray pictures that pinpoint where the sources are. The actual radioactive sources are subsequently implanted and removed once the dosage is administered. A computerised after loading device is used to remotely inject the sources for some treatments.

2.Brachytherapy within the eye's tissue.

This procedure involves inserting radioactive sources into a bodily cavity. Uterine cancer treatment is the most typical case in point. The void left behind after a lumpectomy for breast cancer might potentially be filled with sources. Similar to interstitial brachytherapy, intracavitary brachytherapy is usually only used for a short period of time and uses either remote or manual manipulation of radioactive sources, depending on their intensity.

3.Useful tools for external application.

Inserting radioactive sources into tubes in specially made moulds 0.5 to 1.0 cm from the skin surface allows for tumours that are close to the skin surface to be treated. Compared to external beam approaches, this one might work better on complex, textured exteriors.

Internal radiation treatment, also known as brachytherapy

Radiation is used either adjacent to or within the tumour. Wires, strips, capsules, seeds, and plastic tubes (catheters) are some of the many possible forms that implants might take. Intramuscular placement of the implant is the method of choice. A hospital admission is necessary for internal radiation treatment.

Intrathecal radiation therapy:

tumours of the head and neck, prostate, cervix, ovary, breast, and areas surrounding the anus and pelvis can be treated with these tools, which operate close to the tumour site. A booster dosage of radiation, in the form of either external beam radiation or interstitial radiation, is given to some women who undergo radiation therapy for breast cancer.

Radiation treatment within a hollow or within a duct:

They operate by use of an internal applicator. Uterine carcinoma is the most common indication for this therapy approach. This radiation treatment modality is also being investigated for the treatment of various malignancies, including as those of the breast, bronchus, cervix, gall bladder, mouth, rectum, trachea, uterus, and vagina.

Radioactive material systemic therapy:

Useful for things like strontium 89 and iodine 131. Injecting or orally ingesting these drugs is the usual method of administration. Adults with thyroid cancer or non-Hodgkin's lymphoma may occasionally undergo systemic radiation therapy for treatment. The treatment of various cancers is the responsibility of the researchers. A person's radiation dose is the total quantity of radiation that their tissues receive. The radiation dosage was originally measured in rads until 1985. Grey is the name given to this unit nowadays. Rad is equal to one degree Celsius, while Gy is equal to one hundred degrees. Radiation can have varying effects on various tissues. While the kidneys can only handle 1800cGy, the liver can handle 3000cGy. Typically, a particular cycle of daily doses administered at significantly lower doses makes up the overall amount of radiation (total dose). There is less damage to healthy tissues and more destruction of malignant cells with this operation. A coefficient known as the therapeutic ratio is utilised by the practitioner. In terms of harm to healthy tissues, this coefficient reveals how much harm was inflicted on cancer cells. We can find ways to hurt cancer cells more without hurting healthy tissue any more. The following questions elaborate on these approaches.

Conclusion

Many factors, including the amount of X-ray energy deposited, the radiosensitivity of tumours, and the inclination for DNA repair, influence the therapeutic efficacy of X-ray induced radiotherapy. In this article, we have reviewed and summarised the current state of nanomaterials for RT and RDT, their functional roles in cancer treatment, and the associated therapy techniques in order to create the best possible treatment regimen for X-ray triggered cancer therapy. Several strategies, such as high-Z nanomaterials, combination therapy, tumour microenvironment modulation, and radiation protection, have been inspired by functional nanomaterials as alternatives to conventional radiation therapy. These alternatives address the limitations of traditional RT therapy, such as inadequate tumour X-ray absorption, nonspecific damage to normal cells, reliance on oxygen, and inability to treat metastatic cancer cells. (I) To target tumours using targeted X-ray deposition, a number of classical nanomaterials containing high-Z elements have been created. To successfully sensitise the RT impact for cancer treatment while simultaneously alleviating side effects in normal tissues and organs, this technique relies on the optimal biodistribution and high tumour accumulation of nanomaterials. (II) There may be a synergistic impact when RT is combined with other therapy modalities, such as immunotherapy, chemotherapy, PDT, or PTT, which could increase the therapeutic benefit. Particularly promising would be the prospect of treating metastatic cancer and preventing recurrence when combined with immunotherapy. In order to maximise the synergistic benefit of combination therapy, it is important to understand how the drugs work together and how to best adapt the therapeutic process (including timing, dose, and sequencing) to protect healthy tissues from unwanted side effects. (III) By adjusting the transmembrane oxygen (TMO) pathway through oxygen supply, in-situ O2 synthesis, decreasing GSH concentration, and direct peroxide breakdown, ROS formation can be elevated, which in turn can induce DNA damages, hinder repair, and ultimately lead to a potent ability to kill cancer cells. It should be noted that the chemical reactivity of nanomaterials in tumour may differ from in vitro, which can

affect TME modulation. Therefore, in order to successfully apply the TME-modulation function of nanomaterials, it is crucial to have a thorough grasp of tumour parameters and to regulate many of them simultaneously. (IV) The use of nanomaterials as radioprotectors or nanocarriers for radioprotective chemicals could address the concern about side effects by scavenging ROS in normal tissues. A moderately powerful form of X-ray irradiation could be used to administer RT treatments with the assistance of radioprotectors. The selective and effective protection of normal tissues under X-ray irradiation is a challenging goal to attain in order to increase RT efficacy and prolong survival time for patients. In contrast, recent advances in (i) unitary nanomaterials devoid of additional PSs (MOFs and others) and (ii) nanoscintillators loaded with PSs (NPs based on rare earth elements and metals) have allowed the most recent X-ray triggered treatment modality, RDT, to make rapid strides. When it comes to X-ray triggered cancer therapy, these functional nanomaterials and therapeutic approaches have been effective in increasing therapeutic efficacy while minimising adverse effects. The design of nanomaterials, the mechanism of RT and RDT, and the studies of oncology continue to be significant obstacles on the path to the practical translation of successful cancer therapies. firstly, improving nanomaterial use and biocompatibility. There has been a lot of work on developing X-ray triggered cancer therapies using functional nanomaterials. Nanomaterial toxicity, however, is a major roadblock to clinical translation. Nanomaterials might be biocompatible and active-targeting if modified appropriately, but there would be long-term harmful issues if they were retained in the body. As a result, developing ultrasmall nanoparticles that can pass through the kidneys or biodegradable nanomaterials that contain biocompatible components while still serving their purpose in X-ray triggered cancer treatment is of paramount relevance. In order to optimise the treatment window, it is extremely desirable to build nanomaterials with simultaneous imaging features that can monitor their biodistribution, tumour accumulation, metabolism, and clearance routes. This will allow for long-term toxicity monitoring. 2) Research into the processes involved in reactive oxygen species (ROS) production, whether using oxygen or not. While RT uses electrons to damage cancer cell DNA directly or indirectly, RDT uses X-ray fluorescence or photons to create ROS for lower-dose cancer treatment, both methods take advantage of the physical interaction of X-ray with nanomaterials. But most of them rely heavily on oxygen, which solid tumours don't provide enough of. The energy conversion efficiency of RDT is still limited, despite multiple claims claiming an oxygen-independent method. Therefore, it is crucial to find a solution to the problems of oxygen scarcity and inefficient energy transformation, and to learn how X-ray induced ROS creation with the help of NPs works. (3) Thorough investigations into each of the parameters of the TME. The therapeutic efficacy of radiation therapy (RT) has been enhanced through the use of techniques such as increasing oxygen concentration, breaking down hydroperoxide, and decreasing GSH synthesis, all of which are attributes of the tumour microenvironment. To improve RDT's effectiveness, these tactics show promise as well. However, additional research is needed in oncology to regulate the tumour microenvironment (TME) by alternative means, such as restoring a normal pH, restoring normal vascular, and decomposing the extracellular matrix. 4) Comprehensive analysis of the underlying mechanism of immunological combination treatment. The effective elimination of both local and systemic cancer cells has been demonstrated in numerous pioneering studies using the combination of X-ray triggered therapy with immunotherapy, particularly checkpoint blocking immunotherapy. Therefore, new nanomaterials that promote antitumor immunity could be developed and studied further to inspire concepts for holistic cancer therapy and clinical translation. These materials could integrate X-ray triggered therapy with other immunotherapy modalities.

References

1. Kraft, G. Tumor therapy with heavy charged particles. Prog. Part. Nucl. Phys. 45, S473–S544 (2000). 4. Moss, R. L. Critical review, with an optimistic outlook, on Boron Neutron Capture Therapy (BNCT). Appl. Radiat. Isot. 88, 2–11 (2014).
2. Spiers, F. W. The Influence of Energy Absorption and Electron Range on Dosage in Irradiated Bone*. Br. J. Radiol. 22, 521–533 (1949).
3. Aichinger, H., Dierker, J., Joite-Barfuß, S. & Säbel, M. Radiation Exposure and Image Quality in X-Ray Diagnostic Radiology. doi: 10.1007/978-3-642-11241-6. (Springer Berlin Heidelberg, 2012).
4. Yu, S.-B. & Watson, A. D. Metal-Based X-ray Contrast Media. Chem. Rev. 99, 2353–2378 (1999).
5. Jain, S., Hirst, D. G. & O'Sullivan, J. M. Gold nanoparticles as novel agents for cancer therapy. Br. J. Radiol. 85, 101–113 (2012).
6. Rose, J. H. et al. First radiotherapy of human metastatic brain tumors delivered by a computerized tomography scanner (CTRx). Int. J. Radiat. Oncol. Biol. Phys. 45, 1127–32 (1999).
7. Tamura, M., Matsui, H., Hyodo, I., Tanaka, J. & Miwa, Y. Fluorescence-based co-culture of normal and cancerous cells as an indicator of therapeutic effects in cancer. Eur. J. Pharm. Sci. 63C, 1–7 (2014).
8. Shimokawa, O. et al. Neoplastic transformation and induction of H+, K+-adenosine triphosphatase by N-methyl-N′-nitro-Nnitrosoguanidine in the gastric epithelial RGM-1 cell line. In Vitro Cell. Dev. Biol. Anim. 44, 26–30 (2008).
9. Liapi, E., Georgiades, C. C., Hong, K. & Geschwind, J. F. H. Transcatheter Arterial Chemoembolization: Current Technique and Future Promise. Tech. Vasc. Interv. Radiol. 10, 2–11 (2007).
10. Idée, J.-M. & Guiu, B. Use of Lipiodol as a drug-delivery system for transcatheter arterial chemoembolization of hepatocellular carcinoma: A review. Crit. Rev. Oncol./Hematol. 88, 530–549 (2013).
11. Lo, C. M. et al. Randomized controlled trial of transarterial Lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 35, 1164–1171 (2002).
12. Llovet, J. M. et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet (London, England) 359, 1734–9 (2002).
13. Delaney G, Jacob S, Featherstone C, Barton M: The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer 2005; 104: 1129-1137.
14. Begg AC, Stewart FA, Vens C: Strategies to improve radiotherapy with targeted drugs. Nat Rev Cancer 2011; 11: 239-253.
15. Barnett GC, West CM, Dunning AM, Elliott RM, Coles CE, Pharoah PD, Burnet NG: Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Nat Rev Cancer 2009; 9: 134-142.

16. Bernier J, Hall EJ, Giaccia A: Radiation oncology: a century of achievements. Nature 2004; 4: 737-747.

17. Jackson SP, Bartek J: The DNA-damage response in human biology and disease. Nature 2009; 461: 1071-1078.

18. Bernier J, Hall EJ, Giaccia A: Radiation oncology: a century of achievements. Nature 2004; 4: 737-747.

19. Ellis F: Dose, time and fractionation: a clinical hypothesis. Clin Radiol. 1969; 20: 1-7. 16. International Commission on Radiation Units. Prescribing, recording and reporting photon beam therapy. Supplement to ICRU Report

20. Bethesda: International Commission on Radiation Units and Measurement. MD: ICRU; 1999.

21. Feng FY, Kim HM, Lyden TH, Haxer MJ, Feng M, Worden FP, Chepeha DB, Eisbruch A: Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. Int J Radiat Oncol Phys. 2007; 68: 1289-1298.

22. Wang-Chesebro A, Xia P, Coleman J, Akazawa C, Roach M 3rd: Intensity-modulated radiotherapy improves lymph node coverage and dose to critical structures compared to with three-dimensional conformal radiation therapy in clinically localized prostate cancer. Int J Radiat Oncol Phys. 2006; 66: 654-662.

23. Tipton K, Launders JH, Inamdar R, Miyamoto C, Schoelles K: Stereotactic body radiation therapy: scope of the literature. Ann Intern Med. 2011; 154: 737-745.

24. Lo SS, Moffatt-Bruce SD, Dawson LA, Schwarz RE, Teh BS, Mayr NA, Lu JJ, Grecula JC, Olencki TE, Timmerman RD: The role of local therapy in the management of lung and liver oligometastases. Nat Rev Clin Oncol. 2011; 8: 405-416.

25. Wu QJ, Wang Z, and Yin FF: The impact of respiratory motion and treatment technique on stereotactic body radiation therapy for liver cancer. Med Phys. 2008; 35: 1440-1451.

26. National radiotherapy implementation group report. Stereotactic body radiotherapy; Clinical review of the evidence for SBRT. UK: NRIG. 2010 30. Freeman DE, King CR: Stereotactic body radiotherapy for low-risk prostate cancer: five-year outcomes. Radiat Oncol. 2011; 6: 3.

27. Laramore GE: Role of particle radiotherapy in the management of head and neck cancer. Current Opin Oncol. 2009; 21: 224-231.

28. Schulz-Ertner D, Tsujii H: Particle radiation therapy using proton and heavier ion beams. J Clin Oncol. 2007; 25: 953-964.

29. Ma CM, Maughan RL: Within the next decade conventional cyclotrons for proton radiotherapy will become obsolete and replaced by far less expensive machines using compact laser systems for the acceleration of the protons. Med Phys. 2006; 33: 571-573.

30. Hall EJ: Cancer caused by x-rays-a random event? Lancet Oncol. 2007; 8: 369-370. 35. Baskar R: Emerging role of radiation induced bystander effects: Cell communications and carcinogenesis. Genome Integr. 2010; 1: 13.

31. Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M: Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 1991; 21: 109-122.

32. Verheij M: Clinical biomarkers and imaging for radiotherapy-induced cell death. Cancer Metastasis Rev. 2008; 27: 471-480.

33. Dewey WC, Ling CC, Meyn RE: Radiation-induced apoptosis: relevance to radiotherapy. Int J Radiat Oncol Biol Phys. 1995; 33: 781-796.

34. Rupnow BA, Knox SJ: The role of radiation-induced apoptosis as a determinant of tumor responses to radiation therapy. Apoptosis 1999; 4: 115-143.

35. Cragg MS, Harris C, Strasser A, Scott CL: Unleashing the power of inhibitors of oncogenic kinases through BH3 mimetics. Nat Rev Cancer 2009; 9: 321-326.

36. Fogg VC, Lanning NJ, MacKeigan JP: Mitochondria in cancer: at the crossroads of life and death. Chin J Cancer 2011; 30: 526-539. 42. Eriksson D, Stigbrand T: Radiation-induced cell death mechanisms. Tumour Biol. 2010; 31: 363-372.

37. Sato N, Mizumoto K, Nakamura M, Ueno H, Minamishima YA, Farber JL, Tanaka M: A possible role for centrosome overduplication in radiation-induced cell death. Oncogene 2000; 19: 5281-5290.

38. Vakifahmetoglu H, Olsson M, Zhivotovsky B: Death through a tragedy: mitotic catastrophe. Cell Death Differ. 2008; 15: 1153-1162.

39. Jonathan EC, Bernhard EJ, McKenna WG: How does radiation kill cells? Curr Opin Chem Biol. 1999; 3: 77-83.

40. Hotchkiss RS, Strasser A, McDunn JE, Swanson PE: Cell death. N Engl J Med. 2009; 361: 1570-1583.

41. Roninson I: Tumor cell senescence in cancer treatment. Cancer Res. 2003; 63: 2705-2715.

42. Schmitt CA: Cellular senescence and cancer treatment. Biochim Biophys Acta. 2007; 1775: 5-20.

43. Ito H, Daido S, Kanzawa T, Kondo S, Kondo Y: Radiation-induced autophagy is associated with LC3 and its inhibition sensitizes malignant glioma cells. Int J Oncol. 2005; 26: 1401-1410.

44. Kuwahara Y, Oikawa T, Ochiai Y, Roudkenar MH, Fukumoto M, Shimura T, Ohtake Y, Ohkubo Y, Mori S, Uchiyama Y, Fukumoto M: Enhancement of autophagy is a potential modality for tumors refractory to radiotherapy. Cell Death Dis. 2011; 2: e177.

45. American Association of Physicists in Medicine, D. W. O. Rogers, and J. E. Cygler. 2009. Clinical dosimetry measurements in radiotherapy. Proceedings of the American Association of Physicists in Medicine Summer School, Colorado College, Colorado Springs, CO, June 21–25, 2009. Madison, WI: Medical Physics Pub.

46. Bentzen, S. M., L. S. Constine, J. O. Deasy et al. 2010. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): An introduction to the scientific issues. International Journal of Radiation Oncology Biology Physics 76:S3–S9.

47. Cody, D., and O. Mawlawi. 2008. The Physics and Applications of PET/CT Imaging. Madison, WI: Medical Physics Publ. Corp. Cox, J. D., and K. K. Ang. 2003. Radiation Oncology: Rationale, Technique, Results. 8th ed. St. Louis, MO: Mosby.

48. Ezzell, G. A., J. M. Galvin, D. Low et al. 2003. Guidance document on delivery, treatment planning, and clinical implementation of IMRT: Report of the IMRT subcommittee of the AAPM radiation therapy committee. Medical Physics 30:2089–2115.

49. Hall, E. J. 2000. Radiobiology for the Radiologist. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins.

50. Hall, E. J., and A. J. Giaccia. 2006. Radiobiology for the Radiologist. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins.

51. Hartford, A. C., M. G. Palisca, T. J. Eichler et al. 2009. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) Practice Guidelines for intensity-modulated radiation therapy (IMRT). International Journal of Radiation Oncology Biology Physics. 73:9–14.

52. Hendee, W. R., G. S. Ibbott, and H. G. Hendee. 2005. Radiation Therapy Physics. 3rd ed. Hoboken, NJ: Wiley. International Commission on Radiation Units and Measurements. 1997. Dose and Volume Specification for Reporting Interstitial Therapy.

53. Bethesda, MD: International Commission on Radiation Units and Measurements. International Commission on Radiation Units and Measurements. 1998. Clinical Proton Dosimetry.

54. Johns, H. E., and J. R. Cunningham. 1983. The Physics of Radiology. 4th ed. Springfield, IL: Charles C. Thomas.

55. Karzmark, C. J., and R. J. Morton. 1998. A Primer on Theory and Operation of Linear Accelerators in Radiation Therapy. 2nd ed. Madison, WI: Medical Physics Pub.

56. Khan, F. M., AAPM Radiation Therapy Committee. Task Group No. 25. 1991. Clinical Electron-Beam Dosimetry: Report of Task Group No. 25, Radiation Therapy Committee, AAPM. New York: Published for the American Association of Physicists in Medicine by the American Institute of Physics.

57. Khan, F. M. 2007. Treatment Planning in Radiation Oncology. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins.

58. Marks, L. B., S. M. Bentzen, J. O. Deasy, F.-M. Kong, J. D. Bradley, I. S. Vogelius et al. 2010. Radiation dose–volume effects in the lung. International Journal of Radiation Oncology*Biology*Physics 76(3, Supplement):S70–S76.

59. Metcalfe, P., T. Kron, and P. Hoban. 2007. The Physics of Radiotherapy X-rays and Electrons. Madison, WI: Medical Physics Pub.

60. Otto, K. 2008. Volumetric modulated arc therapy: IMRT in a single gantry arc. Medical Physics 35:310–317.

#

61. Partridge, M., Mi. Ramos, A. Sardaro, and M. Brada. 2011. Dose escalation for non-small cell lung cancer: Analysis and modelling of published literature. Radiotherapy and Oncology 99(1):6–11.

62. Podgoršak, E. B., International Atomic Energy Agency. 2005. Radiation Oncology Physics: A Handbook for Teachers and Students. Vienna: International Atomic Energy Agency.

63. Thomadsen, B., M. J. Rivard, W. M. Butler et al. 2005. Brachytherapy Physics. 2nd ed. Madison, WI: Published for American Association of Physicists in Medicine by Medical Physics Pub.

64. Washington, C. M., and D. T. Leaver. 2004. Principles and Practice of Radiation Therapy. 3rd ed. St. Louis, MO: Mosby Elsevier.

.