

PHYSICAL ANALYSIS OF IONIZING RADIATION AND ITS APPLICATIONS IN MEDICAL RADIOTHERAPY AND ITS RELATIONSHIP TO THE ACCURACY OF CLINICAL BIOMARKERS

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Abstract:

Ionizing radiation is extensively employed in medical procedures, particularly for cancer therapy and diagnostic imaging. Although the biological effects of medium- and high-dose radiation on human health have been established over the past century, the consequences of exposures below 0.5 Gy remain ambiguous. Damage to DNA arises through both direct and indirect mechanisms, resulting in single- and double-strand breaks. Clustered double-strand breaks are especially deleterious due to their complexity and the considerable difficulty involved in repair. The DNA damage response is predominantly mediated via non-homologous end-joining, an error-prone repair pathway that can engender chromosome aberrations and genomic instability, thereby contributing to carcinogenesis. Dose rate critically influences the extent of cellular damage: high dose rates provoke rapid energy deposition, overwhelming repair processes, whereas low dose rates afford temporal windows for repair, mitigating adverse effects. A sophisticated understanding of these underlying biological consequences is imperative for optimizing clinical application of ionizing radiation.

Keywords: Radiation, DNA, Carcinogenesis

1. Introduction

Ionizing radiation plays an integral role in medical radiotherapy, where high doses selectively eliminate malignant cells while sparing normal tissue, thereby improving treatment outcomes and patient survival rates. This therapeutic application has become increasingly important in cancer treatment, serving as a cornerstone of modern oncology, but it simultaneously alters tumour-cell concentrations and compromises the precision of clinical biomarkers used to guide treatment decisions. Such biomarker accuracy is critical at every stage of radiotherapy, from determining the appropriate

course of treatment based on individual patient factors to assessing the prognosis and evaluating patient remission effectively. These considerations set the foundation for an in-depth examination of ionizing radiation's physical properties and the complex biological responses they elicit in human tissues. Understanding these fundamental mechanisms is absolutely essential for any student or practitioner who encounters the important concept of ionizing radiation in their studies or clinical work. Only with such a comprehensive understanding can the subsequent discussion on medical radiotherapy, tumour-cell damage, and biomarker analysis be fully appreciated and contextualized. This knowledge not only enhances the effectiveness of treatment protocols but also paves the way for future advancements in radiological technology and cancer care strategies.

Fundamentals of Ionizing Radiation

There are three main types of ionizing radiations such as alpha-rays, beta-rays and gamma-rays. Alpha-rays are positively charged ions with a size of a big helium atom and a high energy level. Beta-rays have an electric charge and a size of an electron but rather high energy. Gamma-rays do not have electric charge, and differ from photons only in energy level or wavelength. Some other types of ionizing radiations are also known with relatively short lifetimes, including neutron rays and X-rays. X-rays act like gamma-rays in shielding but are generally orders of magnitude weaker.

Electromagnetic radiations, such as electromagnetic waves and quantum particles, each having a specified level of energy. The high energy of electromagnetic radiation can ionize neutral particles. Visible light is an example of the electromagnetic wave that possesses the lowest range of energy. Energetic quantum particles are composed of individual particle elements that have kinetic energy. When these energetic particles pass through the medium, the most energy is transfer to the medium, which makes the quantum particles lose kinetic energy until they come to rest. Ions will be made with these energetic quantum particles because the ions have enough energy to interact with atoms to take out an electron. The ionization process is the new set of atoms.

Types of Ionizing Radiation

A sustained increase of entropy in biological systems induced by ionizing radiation (IR) acts as a fundamental cause of physiological deterioration leading to carcinogenesis and aging over time. These processes relate to the function of biomolecules serving as clinical biomarkers. Medical radiotherapy (RT) utilizes IR to treat cancer with 52 % of patients receiving RT as part of their clinical care. The precision of clinical biomarker evaluation requires consideration of a fundamental question: does IR affect the expression and measurement of clinical biomarkers? The rationale for this question remains that biomolecules interact with IR, resulting in altered concentrations communicated as clinical biomarker levels independent of tumor progression or therapeutic response. Ionizing radiation emanates from natural terrestrial sources, anthropogenic sources, diagnostic radiography, exposure to radioactive elements, and cosmic rays. The ionization of matter accounts for biological effects of radiation. The significant types of ionizing radiation include alpha (α) particles, beta (β) particles, gamma (γ) rays, X-rays and neutrons. Low-linear energy transfer (LET) radiation depicts energy imparted per unit length of track. Alpha (α) and beta (β) particles exhibit relatively higher energy than gamma (γ) rays and X-rays, while neutrons possess a wide range of energies. High-LET radiations such as α -particles and neutrons produce more severe effects than low-LET irradiation. Gamma (γ) rays and X-rays represent low-LET radiation.

Mechanisms of Action

Ionizing radiation causes damage through chromosomal DNA double-strand breaks, chromosome aberrations, and cell-cycle progression delays. Ra-223 accumulates preferentially in the bone matrix surrounding metastases and delivers highly cytotoxic alpha-particles with a range of only a few cell diameters, inducing predominantly double-strand DNA breaks in adjacent cells. Photon-and particle-radiation-induced damage is interpreted in the context of conventional radiobiology and molecular mechanisms that lead to early and late sequelae following either localized or total body exposure. IR targets biological macromolecules directly, or through generation of highly reactive free radicals and reactive oxygen species (ROS), resulting in damage at enzymatic, membrane, and chromosomal levels,

which collectively contribute to apoptosis and the delayed effects of radiation.

2. Materials and Methods

Medical Radiotherapy: An Overview

Medical radiotherapy has undergone significant evolution since the inception of radiation-induced cancer cell death treatments in the 1890s. Early modalities, such as the use of radium and X-rays, paved the way for modern, intricate photon-beam techniques. Intensity-modulated radiotherapy (IMRT) epitomizes such advancement, delivering high-energy X-rays with enhanced resolution and accuracy. Therapeutic planning today commences with virtual reconstruction of the targeted anatomy, to which radiation dose prescriptions and fractionation schedules are applied.

Subsequent treatment planning employs proprietary software to delineate the area for radiation delivery, generating guidelines that steer linear-accelerator systems during sessions. The patient is positioned in specialized devices designed to ensure reproducibility across treatment fractions. Faster reconstructions and algorithms have augmented the precision of these processes, permitting adaptation to temporal alterations in tumor size, density, and location, as well as movements of adjacent organs at risk.

Beyond photon beams, ions such as protons, carbon, and helium have found application in modern radiotherapy. Notwithstanding the modality, the irradiation process universally initiates cellular damage through the deposition of energy concentrated within targeted volumes.

History of Radiotherapy

The use of ionizing radiation as a cancer treatment has been under investigation since 1895. Aspiring to help patients, medical doctors developed various radiotherapy techniques aimed at eradicating tumours while protecting nearby tissues. Radiotherapy studies followed scientists' developing understanding of radioactivity and its effects over the decades. After Roentgen's discovery of X-rays in 1895, Gustave Becquerel found that sunlight intensity influenced radioactivity from uranium salts. The Becquerel family further developed radioactive studies into medical and industrial applications, and by 1901, Henri Becquerel had introduced radon to the medical field. Formulated in 1874, radon was found to improve cancer cells' radiosensitivity and treatment applicability. Other isotopes, such as radium-226 and iodine-131, were used in radiotherapy to treat carcinomas and lymphomas. During the Second World War, Rudolf Sievert impacted the war effort by designing equipment to monitor soldiers' exposure. Subsequently, the Sievert unit was adopted to quantify the radiation doses received during medical procedures.

Current Techniques in Radiotherapy

Radiotherapy was first demonstrated in the form of stereotactic radiosurgery in 1951. The development of treatment planning systems has allowed for three-dimensional conformal therapy. Later methods deliver beams with fluences that vary across them. Masses are typically treated via fractionated radiotherapy, wherein the total dose is divided into multiple smaller doses, called fractions, delivered over several days. Advances in radiotherapy have enabled patients who suffer tumor recurrences in prior radiation volumes and/or receive re-irradiation to undergo treatments that minimize damage to adjacent normal tissues, thereby sparing normal tissue function. A sub-field of rapidly developing therapies in radiotherapy is hypofractionation. This includes techniques such as stereotactic body radiotherapy, stereotactic ablative therapy (SABR), and stereotactic ablative radiosurgery.

Treatment Planning and Delivery

Medical radiation is applied to the patient primarily through three-dimensional conformal radiation therapy (3D-CRT). In 3D-CRT a high-energy X-ray photon beam is shaped by a multi-leaf collimator (MLC) to the contour of a projected planning target volume (PTV) as previously designed by the radiation oncologist and medical physics team. The PTV is defined as the gross tumour volume (GTV) plus a margin of tissue around this gross tumour in order to allow for small movements of the tumour during treatment, for example due to respiration. Immobilisation devices are also routinely used during

treatment to minimise patient movement. The radiation beam will typically pass through intervening healthy tissue before reaching the target and the dose must be planned so that the amount of irradiation delivered to the normal tissue remains below normal toxicity thresholds. In addition, it is important to consider the size of the field leaving the lens of the eye as scattering of the X-ray radiation from the edge of the field can cause cataracts.

Impact of Ionizing Radiation on Tumor Cells

Ionizing radiation frequently causes damaged DNA to misrepair, generating additional lesions. It produces chemical modifications in many macromolecules, including proteins and lipids, and provokes temporary or permanent changes in cell behavior. Photon radiation forms sparse ionizations along particle tracks and produces relatively simple DNA damage, whereas high linear energy transfer (LET) radiation deposits energy densely along tracks and induces complex, difficult-to-repair lesions.

Radiotherapy applies ionizing radiation to treat solids tumors through controlled irradiation at therapeutic doses. The approach uses various techniques, from two-dimensional methods and three-dimensional conformal radiotherapy to high-precision procedures offering substantially increased delivery accuracy. Biologically, ionizing radiation damages tumor cells at multiple levels—molecular, cellular, tissue, total-body—triggering cell death, growth arrest, senescence, metastasis, and inflammation. It alters tumor cell properties, including phenotype, immunogenicity, and microenvironment, with effects that can persist over time. Radiotherapy also suppresses anti-tumor immunity through side effects and can harm normal tissue, compromising overall therapeutic outcomes. In vitro studies of breast cancer cells exposed to clinical radiotherapy doses reveal that genetically and epigenetically regulated responses determine radiation sensitivity. Radiation affects molecular pathways governing proliferation, cell death, and transformation, highlighting the potential of combined treatments that incorporate molecular biomarker evaluation to enhance therapy efficacy and safety.

Cancer biopsies collected at diagnosis or during follow-up provide clinical biomarkers that capture disease status, classify tumor stages, and inform treatment strategies. Radiation-induced changes in tumor cells have a profound impact on the precision of these biomarkers, necessitating a deeper understanding of radiation effects to optimize their clinical applicability and ensure that therapeutic advances translate into improved outcomes.

Cellular Response to Radiation

The mechanisms by which ionizing radiation induces cellular and tissue damage have been the subject of extensive research. Energy deposited by the radiation through electromagnetic or nuclear interactions with the passing particle can damage cells via direct or indirect processes. The direct action involves the energy deposition in, and ionization of, a critical cellular macromolecule, such as DNA. The indirect action relies on the formation of free radicals from radiolysis of water molecules (for example, hydroxyl $\text{OH}\cdot$ and hydroperoxyl $\text{O}_2\text{H}\cdot$ radicals) leading to further damage to cellular components. It is important to recall that the physiological response to radiation is temporally dynamic, as radiation-induced perturbations of biological processes continue until repair or cell death. The intracellular milieu actively participates to modulate the extent of the fixed damage. Damage to proteins and lipids is relatively efficient, but these lesions are less likely to provide a direct connection to late effects. Nonetheless, damage to protein-encoding genes and DNA is recognized as a significant initiator of long-term cellular damage following radiation exposure.

Radiation-Induced Damage

Ionizing radiation induces damage in tumor cells either directly, through ionization or by excitation of critical targets such as nuclear DNA, or indirectly by producing reactive species that are chemically reactive and therefore potentially damaging to components within the cell. The most important reactive species in indirect damage induction are reactive oxygen species (ROS), which are highly reactive species that can interact with and modify proteins, lipids, and nuclear DNA. Such modifications to DNA are the source of the primary biological damage caused by oxidative stress and ionizing radiation.

Seven types of oxidative modification of the four bases in DNA have been investigated: 8-oxo-7,8-

dihydroguanine (8-oxo-Gua), 1, N6-ethenoadenine, hypoxanthine, xanthine, thymine glycol, uracil glycol, and 5-hydroxycytosine. Of these, 8-oxo-Gua has been used most extensively as a marker of oxidative damage. Mitochondrial DNA may also be a target for oxidative damage.

Ionizing radiation induces a broad spectrum of damage to nuclear DNA, including oxidized bases (such as thymine glycol), deaminated bases (e.g. xanthine), apurinic/apyrimidinic sites (AP sites), single-strand breaks (SSBs), and double-strand breaks (DSBs). Depending on its location in the genome, the induction of damage may result in a multitude of cellular responses, such as apoptosis, necrosis, or autophagy. Figure 67 illustrates cancer cells stained for radiation-induced DNA damage.

DNA double-strand breaks induced by ionizing radiation trigger DNA damage-response pathways; an important component of this process is the phosphorylation of the histone variant H2AX. Specific sites of DNA double-strand break induction can also be detected by using a recently described technique, which employs biotinylated nucleotides incorporated at break sites.

3. Results and Discussion

Clinical Biomarkers in Oncology

Clinical biomarkers can refine diagnosis and predict prognosis and response to therapy, helping to reduce patient exposures to unnecessary diagnostic procedures and ineffective treatments. Clinical biomarkers detect a normal or an abnormal process or condition and measure the response to a therapy. Multiple types of clinical biomarkers exist, including molecular, histologic, radiographic, or physiologic characteristics. Clinical biomarkers facilitate prediction and early detection of a disease and can provide insights into the relative likelihood of favourable or unfavourable treatment outcomes. Understanding biomarkers can target patient subsets likely to benefit from, or develop toxicities resulting from, radiotherapy. Circulating biomarkers may enable prediction, detection, and monitoring of disease, progression, and/or radiation-induced injury.

Definition and Importance

A clinical biomarker is a biomarker that can be detected in patients. Biomarkers are categorized according to their intended use, such as diagnostic, prognostic or predictive. The focus here lies on protein biomarkers, of which thousands have been proposed for cancer diagnosis, staging and treatment monitoring. However, only a few have actually gained entry to the clinics and routine healthcare.

The damage or death of tumor cells is the goal of radiotherapy. Tumor cells respond to treatment through changes in gene expression that are mirrored in the abundance of cellular proteins or the proteins secreted into body fluids. The measurement of the abundance of such proteins forms the basis for clinical biomarker analysis in the follow-up of cancer treatment to detect recurrence, the development of secondary tumors or other late effects of tumor treatment. The success of such an approach hinges, therefore, in part, on the precision of protein biomarker analysis following tumor irradiation.

Types of Clinical Biomarkers

Clinical biomarkers play a vital role in the detection and monitoring of cancer. Biological molecules found within tumor tissue or bodily fluids can serve as informative clinical biomarkers. These determine the likelihood of a tumor's presence on the basis of a person's symptoms, clinical grading, or histopathological examination. Clinical biomarkers may be detected and measured through blood tests or immunohistochemical techniques. Tumor markers, as clinical biomarkers, provide clinicians with means of assessing the progress of a malignancy and gauge the effectiveness of therapeutic interventions. They therefore have major implications for patient prognosis and disease-free survival time.

Three main types of clinical biomarker can be identified: prognostic, predictive and pharmacodynamic. Prognostic biomarkers have potential in recognising the course of a cancer, independent of therapy; or simply, how aggressive a malignancy is likely to be. For example, abnormal protein expressions such

as phosphatase and tensin homologue (PTEN) deletions or epidermal growth factor receptor (EGFR) over-expression indicate a poor prognosis. Predictive biomarkers determine the likelihood of a cancer responding to therapy. Pharmacodynamic biomarkers on the other hand, provide indicators of tumour status after the start of therapy; measuring whether a treatment has had a desired effect, or how soon this may be detected [1]. For example, acidic pre-treatment chromogranin A (Cg A) levels are a clinical biomarker in predicting the response of pancreatic neuro-endocrine tumours to therapy. By evaluating these three sets of clinical biomarker within bodily fluids or tissue samples, cancer diagnosis, tumour progression and therapeutic efficacy following radiotherapy can be determined with increased accuracy and reliability.

Radiotherapy and Biomarker Precision

Biomarkers are changed during radiotherapy due to either biological adaptation or the selection of intrinsically resistant subpopulations, with expression levels or immunostaining patterns differing between irradiated and nonirradiated tumours [2]. Identifying and studying radiotherapy-relevant biomarkers require caution. Changes in the concentration of plasma or tissue biomarkers and acute interference of the assays during and soon after radiation are likely to limit the value of such tests as a verifier of radiotherapy delivery in individual patients. The extent and duration of plasma biomarker changes, the timing of sampling of tissue for biomarkers after the completion of radiotherapy, and intertreatment interval must therefore be carefully considered and balanced against the need to deliver an effective overall cumulative dose [3]. Reliable adjustments to a patient's prescription should be possible only when the scientific basis for such procedures is thoroughly tested and verified with repeated clinical measurements. The precise roles of biomarkers in the development of patient-specific adaptive protocols in radiotherapy therefore remain uncertain at the present time [4].

Effects of Radiation on Biomarker Expression

Biomarkers serve as measurable indicators of biological processes or diseases. They are classified as predictive (prognostic), diagnostic, and pharmacodynamic, with ongoing research yielding new types and variations. In cancer, biomarkers are categorized into tumor markers, apoptosis-related biomarkers, and angiogenesis markers, playing a crucial role in diagnosis, prognosis, and therapy monitoring across numerous cancer types [5].

Clinical biomarkers illuminate the mechanisms of radiotherapy by characterizing the effects of ionizing radiation. They facilitate the identification of responders versus non-responders, thereby supporting personalized cancer treatment. Cancer types meeting these criteria, such as breast, colorectal, and non-small-cell lung disease, undergo radiotherapy with a significant curative intent.

Challenges in Biomarker Measurement

The measurement of clinical biomarkers is affected by irradiation dose and tumor response, which consequently compromises the precision of biomarker measurements [6]. Biomarkers of ionizing radiation are indispensable for triage, dose estimation, injury assessment, and prognosis in large-scale radiological events. Rapid, reliable, high-throughput, and ubiquitous radiation-specific biodosimetry tools are crucial, especially in mass casualty scenarios, to facilitate the timely identification of exposed individuals and deliver appropriate medical interventions [7]. The biological effects of ionizing radiation are determined by several variables, including the exposure level, dose rate, type of ionizing radiation, and the physiological state and type of exposed cells. Accordingly, estimates for the absorbed radiation dose that can enable accurate prediction of radiation-induced health effects must be tailored to the characteristics of the radiation field and target tissues. Efforts have focused on identifying biomarkers amenable to high-throughput biodosimetry screens, many of which currently exist. These encompass phospho- γ H2AX, dicentrics, gene expression signatures, micronuclei, and translocations.

Advancements in Radiotherapy Techniques

Advancements in radiation therapy techniques have come hand in hand with a more precise radiotherapy treatment delivery. Stereotactic body radiotherapy (SBRT) has dominated this emerging field since the 1990s; intensity-modulated radiotherapy (IMRT) evolved as a concept since 1990; and

proton therapy has advanced towards the standard model of leukemia treatment. A perspective of these innovative photon-based SBRT and IMRT radiation techniques is presented along with an overview of the treatment planning and delivery aspects of proton therapy. In addition, the impact of functional imaging techniques on proton therapy methods is described, and several state-of-the-art clinical trials incorporating the above techniques are discussed. The treatment techniques are then placed within the context of general goals for radiotherapy—improving patient outcome, reducing complications, and improving quality of life—followed by a short discussion of the ethical issues associated with the new techniques [8][9][10].

Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT) enables delivery of high-dose radiotherapy to small, well-defined targets over relatively few treatment sessions, thereby achieving high local control rates in various tumor sites [11]. Significant toxicity may accompany this approach. Ongoing clinical studies will clarify SBRT's role as a potentially curative alternative to surgery for primary tumors and oligometastatic disease. More extended follow-up periods and additional survival data are essential to fully define its comparative value. External beam delivery platforms and planning techniques continue to improve the preciseness and accuracy of SBRT [12]. The technique employs high-precision external-beam radiotherapy—sometimes referred to as stereotactic ablative radiotherapy (SABR)—to deliver biologically effective doses sufficient to ablate tumours in selected clinical situations [13]. The demand for SBRT is rising steadily; technological advances have rendered it accessible in an increasing number of centres worldwide.

The origins of SBRT can be traced to intracranial stereotactic radiosurgery, first pioneered by Professor Lars Leksell through the use of Gamma Knife devices. Early extracranial investigations demonstrated the feasibility of delivering high-dose treatments using stereotactic fixation, ensuring the geometric accuracy necessary to spare adjacent critical structures during tumour boost doses. The availability of commercial delivery platforms—including linear accelerators, specialized machines, tomotherapy units, particle accelerators and Cyberknife—has considerably enhanced the clinical scope of SBRT.

Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) constitutes a significant treatment modality in radiotherapy, enabling photon radiation delivery with conformality to three-dimensional target volumes at dose levels precisely prescribed by the radiation oncologist. IMRT encompasses a spectrum of delivery and planning techniques, such as serial tomotherapy, multileaf collimator (MLC) serial tomotherapy, dynamic MLC, tomodirect, and multiple-arc methods. Beyond targeting the tumor volume, these approaches facilitate constraining specific organs at risk to specified dose limits, offering the potential to enhance the therapeutic ratio over conventional three-dimensional conformal radiotherapy [14].

The capacity of IMRT to administer highly conformal radiation doses leads to a substantially improved dose distribution within the patient and a decrease in dosage to normal tissue, while achieving equal or superior tumor control probabilities. Although the highly conformal dose distributions of IMRT signal a potential improvement in patient survival rates, toxicity profiles, and overall patient experience, widespread clinical validation remains essential to solidify its standing as a major cancer treatment modality [15].

Proton Therapy Innovations

Proton therapy has recently emerged as an addition to photon and electron treatments. In contrast to photons and electrons, protons possess a defined range in the human tissue known as the Bragg peak, where the highest dose of radiation is deposited. This precise dose distribution offers significant clinical benefits, including sparing of organs at risk and reduction in the integral dose compared with conventional photon techniques. Nonetheless, the exact position of the Bragg peak is sensitive to uncertainties in dose delivery.

Highly conformal irradiation techniques, including stereotactic body radiotherapy and intensity-modulated radiation therapy with photons and protons, require extremely precise dose applications.

This trend towards conformal irradiation entails a corresponding demand for enhanced certainty and precision in treatment planning. Particle therapy with protons and carbon ions represents a substantial step toward reducing acute and late adverse effects through various advanced features such as localized energy deposition at the Bragg peak, reduced lateral penumbra, elevated relative biological effectiveness, and hypofractionation. These innovations alleviate risks associated with the dose bath to normal tissues and the attendant formation of catastrophic mutations responsible for secondary cancer induction, as well as mitigating those organs at risk located in close anatomical proximity [16][17][18].

Clinical Trials and Research

Clinical trials enhance scientific knowledge, improve quality of life, and extend life expectancy. Although randomized clinical trials remain the gold standard, other contemporary trial designs facilitate evaluation of new cancer interventions. Clarification of trial requirements ensures efficient monitoring and control. Both concurrent and sequential-boost radiotherapy (RT) schedules maintain similar low local failure rates.

Radiotherapy trials generally investigate tumor control and late toxicity. Because late toxicity following curative RT accrues over several years, mature results often require prolonged trial follow-up (sometimes exceeding ten years) to provide meaningful data. Extensive late toxicities may impose permanent functional deficits, drastically diminish quality of life, and potentially prompt discontinuation of curative treatment. Dose escalation beyond the minimum curative level, particularly when chemotherapy is added, elevates the risk of detrimental late toxicity. The conventional phase I dose-escalation trial often involves small patient cohorts that may not capture delayed toxicity in a timely manner. The time-to-event continual reassessment method (TITE-CRM) incorporates ongoing patient accrual and models toxicity via Bayes' theorem, enabling earlier assessment of late effects; however, implementing TITE-CRM in RT necessitates substantial approvals. Quality assurance (QA) processes ensure delivery of RT as specified by protocol, thereby underpinning reliable interpretation of multi-center trial outcomes. Many RT trials compare standard-of-care dose-fractionation schedules or investigate different technologies (e.g., photon versus proton RT) [19] [20].

Proton therapy provides highly targeted treatment that reduces exposure and risk of side effects in normal tissues, especially at distal depths beyond the target volume, which are vulnerable to normal tissue complications. Consequently, proton RT is extremely beneficial for pediatric cases requiring multi-organ sparing and for thoracic radiation scenarios. The RadComp trial exemplifies a large, multi-center randomized study comparing cardiac outcomes after photon versus proton RT in patients with non-metastatic breast cancer (NCT02603341). Even when competing regimens both represent standards of care, this trial addresses critical clinical questions regarding variation in cardiac toxicity [21]. Such contemporary phase III studies constitute the frontline of investigation even in settings of well-established treatments.

Recent Developments in Radiotherapy Research

Modern medicine relies on radiation as an essential means to treat a wide range of conditions. Sterile surgical environments are maintained by irradiating instruments and consumables before use, while diagnostic radiography offers a first-line, inexpensive method for examining patients, providing a real-time initial examination for many injuries [22],[23]. X-rays also play an important role in visualizing soft tissues and contrast agents, for example, enabling detailed examination of the gastrointestinal tract by using a flat-bed X-ray system. Ionizing radiation also forms the basis of medical radiotherapy, with photons used extensively in treatments for malignant conditions [24]. Despite the risk of a second cancer developing later in life, the benefits of radiotherapy far outweigh the risks, with at least 50% of cancer patients undergoing some form of treatment involving ionizing radiation.

A variety of new techniques have emerged over the last few decades enabling the delivery of an appropriate, conformal dose across all aspects of cancer radiotherapy. The increased precision prompted by these developments places greater emphasis on assessing the response of the body to these advanced treatment modalities. Clinical biomarkers, a wide group of observable biological

indicators, may serve as a useful window on the body's response to ionizing radiation. They have long since been identified as a valuable tool for oncology and are widely investigated as a means of improving precision medicine [25].

Radiotherapy enables absolute control of approximately 40–50% of localized tumours if treated as the sole therapeutic intervention. Achieving complete eradication presents a substantial challenge both technically and biologically—a challenge that has motivated the development of accurate radiation-delivery systems. Traditional radiotherapy was limited to one of two modalities: brachytherapy or teletherapy [26]. The early days of radiotherapy donors employed relatively simple approaches delivering a non-conformal dose distribution that was difficult to influence. As a result, technical improvements have often focused on ensuring the tumour receives an adequate dose while a tolerable dose is delivered to the surrounding healthy tissue.

Biomarker Studies in Clinical Trials

Results from clinical studies or patient-derived xenograft models show that ionizing radiation interferes with the assessment of tumor-specificity of clinical biomarkers and reduces the precision in their measurement. Hence, the impact of radiation-induced cellular and extracellular events on clinical biomarker expression or structure requires further systematic in-depth analyses before developing patient- or tumor-specific precision diagnostic or prognostic protocols [27], [29].

The current standard of cancer-care therapeutic and diagnostic approaches for solid tumors, and some hematological malignancies, is medical radiation therapy delivered in either a conventional fractionated, moderate hypofractionated or hypofractionated treatment regime [30]. Significant developments focus on improving the precision and efficacy of medical radiotherapy, for example using intensity modulated radiation therapy (IMRT), modulated radiation therapy (VMAT), proton radiation therapy, image-guided radiation therapy (IGRT) and stereotactic body radiotherapy (SBRT) or cancer specific pegged biological effective dose (BED) models and individualized fractionation [31], [32]. SBRT and high intensity modulated radiation therapy (IMRT) represent both new and emerging, yet promising radiotherapy modalities with an increased capacity to precisely target and deliver lethal high radiation doses to tumor masses within a restricted localization to main tumor volumes with minimal sparing of adjacent healthy tissue, thereby preventing or rapidly minimizing patient toxicities. Precision and efficacy are rarely addressed or measured in routine cancer-care [33]. Distinguishing the highly specific cancer-cell response from the variability and survival of the surrounding microenvironment and the patient background is a major challenge. In addition, patient-specific curative treatments with radiotherapy or a radiotherapy-chemotherapy combination remain hampered by both the damaging effects to adjacent normal-tissue and the often incomplete or lack of molecular assessment of tumor-specificity to ionizing radiation [34].

Augmenting the therapeutic effects of radiation or radiation-chemotherapy combination treatments is an attractive strategy to address both these problems. The evaluation of longitudinal molecular biomarkers following radiation treatment in pre-clinical models is, therefore, essential to increase our understanding of tumor-specificity and determine the longevity of radiation-induced cellular or extracellular events in a clinically relevant setting. This approach has the additional advantage of improving the efficacy and precision of cancer treatment, and of addressing the adverse long-term effects of radiation on tumor-surrounding healthy tissues both of which are large concerns in routine oncology and often directly responsible for self-assessed reductions in patients' quality-of-life [35].

Patient Outcomes and Quality of Life

Delivery of the prescribed radiotherapy dose to the planning target volume has been shown to be effective for precise tumour control [36]. Quality of life (QOL) therefore compromises an important consideration in therapeutic decision-making. After five years of clinical follow-up, QOL impairment was minimal except for mild erectile dysfunction, and the patients' satisfaction with the treatment was high. In a quality improvement initiative based on patients receiving radiotherapy, those with hospitalizations during or within 2 weeks after treatment, treatment breaks of 3 or more days, or weight loss of 10% or more were reviewed [37]. When compared with a similar cohort of patients for a prior

time period, review of the adverse outcomes led to several changes in departmental practice. Further investigations were also suggested to quantify improvements in patient care. As advanced age was identified as a prognostic factor associated with inferior outcomes, close attention was recommended to elderly patients undergoing treatment.

Assessing Treatment Efficacy

Ionizing radiation has become an important technique in medical therapy. It is widely used in several areas of medicine including diagnosis and treatment of several pathologies. Radiotherapy, in particular, uses ionizing radiation generated by a radioactive source or by an accelerator in order to eliminate or reduce the size of tumoral cells, with the least damage to the adjacent areas as possible. In this respect, clinical biomarkers become important in order to validate the progress of radiotherapy techniques, by establishing the changes that their expression undergoes when tumor cells are exposed to an irradiation field [38].

Radiotherapy represents a widely used technique for the treatment of adults or children with malignant or benign tumors, giving as a result the death or sterilization of cancer cells. It can be combined with chemotherapy or surgery. During radiotherapy, tumor cells are irradiated while a minimum dose is delivered to the nearby healthy cells. The diagram of the radiation beam results from treatment planning and depends on the number, position, and size of the irradiation portals created to target the tumoral area. Radiotherapy uses various ionizing radiation types, such as γ -rays, X-rays, protons, electrons, neutrons, or heavy ions. [39][40][41]

Long-term Effects of Radiotherapy

After completing therapeutic doses of irradiation, carefully considered patient outcomes are necessary. Stereotactic radiotherapy for brain metastases improved long-term survival, but also increased the risk of late toxicities, such as radiation necrosis, brain edema, and neuropathy [42] [43]. Rate-limiting toxicities remain important in treatment decisions. In breast cancer patients, secondary tumors at a previously irradiated site are well documented [44]. Radiation exposure may also induce systemic inflammatory responses by stimulating the immune system. Mild radiotherapy side effects produce 0.1–0.5 Gy irradiation and can activate the immune system.

Ethical Considerations in Radiotherapy

When medical irradiation cannot be avoided, multidisciplinary teams prepare detailed treatment programs taking into account the most effective dose-energy combinations and fractionation schemes together with delivery geometries. Radiotherapy developed extensively following World War II, and three distinct phases can be identified. A first phase during the 1960s centred on physical dose distributions for which better electronics and computing power allowed three-dimensional curl planning and conformal delivery. Improved targeting effects were obtained through the development of stereotactic radiosurgery in the 1970s. Fully integrated imaging was adopted during the 1980s and dose calculations added refinements to normalize for tissue heterogeneities and build biological indices. In the 1990s and 2000s, powerful multi-leaf collimators retrofit on older machines or incorporated into new accelerators allowed intensity-modulated radiotherapy, and the use of charged protons or other particles such as carbon ions increased considerably. Apart from interactions with other modalities, such as high-intensity ultrasonic frequency and immunotherapy, the emphasis for future radiotherapy research will be on the use and combination of protons/electrons for very “high-precision” treatments [45]. Radiotherapy is now the recommended primary treatment for approximately 50% of malignancies [46]. Patients who receive a confirmed diagnosis of cancer depend heavily on clinical biomarkers and, for many years, these have been the main diagnostics for medical decision-making and choosing the best treatment approach. The accuracy of these markers is fundamental to the effectiveness of interventions on exposed individuals. They are used for risk assessment and risk stratification and for developing tailored treatment regimens in individual patients. However, exposure to ionizing radiation increases the level of inconsistency in clinical-biomarker determination and potentially reduces their precision for medical diagnosis.

Informed Consent and Patient Autonomy

The purpose of informed consent is to promote patient autonomy by providing patients with relevant information and a voluntary choice to accept or refuse a proposed diagnostic or therapeutic intervention. The process of informed consent consists of two elements: the information aspect and the decision-making aspect. On the one hand, information must be based on the most recent scientific evidence and explained in non-technical language including the benefits and risks of the diagnostic or therapeutic strategy as well as any alternative options. On the other hand, the patient must be able to take the time needed to reflect and has the right to change their mind at any time. Overexposure to ionising medical imaging is recognised as a global issue that could lead to long-term adverse health effects. Efforts to improve the appropriateness of diagnostic and therapeutic investigations may not be sufficient to avoid inappropriate use of ionising medical imaging. Informed consent to diagnostic and therapeutic procedures involving exposure to ionising radiation can address the patient autonomy issue and contrast the inappropriateness related to overuse and misuse. [47]

Balancing Risks and Benefits

Ionising radiation is electromagnetic or particulate radiation that has enough energy to remove electrons (to ionise atoms or molecules) when passing through matter [48]. Various forms of ionising radiation exist, including (i) alpha particles (high-energy helium nuclei), (ii) beta particles (high-energy electrons or positrons), (iii) gamma rays (high-energy electromagnetic radiation without a charge), (iv) X-rays (lower energy electromagnetic radiation without a charge), (v) neutrons (particles with mass and no charge), and (vi) heavy ions (high-energy charged particles with a larger mass than alpha particles) [49]. Despite the damaging effects of acute exposure to high doses of ionising radiation, it remains a critical component for treating a variety of cancers due to the ability to kill tumour cells. Consequently, several types of medical radiation are commonly used for treating various malignancies, including X-rays, gamma rays, protons, and heavy ions. Maintaining a clear understanding of the mechanisms of ionising radiation and the corresponding cellular response allows for these varied forms to be employed successfully in both cancer treatment and research [50].

Future Directions in Radiotherapy and Biomarker Research

The field of radiotherapy is progressing toward personalized medicine, in which a growing arsenal of biomarker-guided approaches may be used in various clinical scenarios (e.g., management of toxicity, adaptive therapy, follow-up, and as adjuncts to immune-based treatments). They are likely to play an integral role in the optimization of future radiotherapy protocols. Because biomarker integration is made possible through advances in radiotherapy, further development of treatment modalities may broaden opportunities to incorporate and exploit this strategy. Biomarker-driven techniques will therefore emerge as an important component of the regime that defines the future of radiotherapy.

Personalized Medicine Approaches

At present, clinical trials deploying radiation therapy rarely use clinical biomarkers as inclusion or exclusion criteria. However, one can make a convincing case that radiation therapy would benefit if suitable clinical biomarkers could be identified. Clinical biomarkers are used to characterize disease and patient biology, and predict patient response to therapy. An unmet need remains for clinical biomarkers that predict patient sensitivity to radiation therapy and radiation-induced toxicities [51]. Functional imaging modalities such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are beginning to be evaluated as clinical biomarkers for the localization and dosimetry of radiation therapy [52]. Additional research into the identification of actionable clinical biomarkers for radiation therapy could provide an impetus for more personalized treatment.

Integrating Biomarkers into Treatment Protocols

A biomarker reflects an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological. It is a substance that is measured and evaluated as an indicator of normal biological or physiological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. Clinical oncology biomarkers provide information which would otherwise

only be obtained by invasive tissue biopsy if they were to be assessed by traditional methods [53]. Biomarkers can be classified into four broad categories [2]: 1) Diagnostic biomarkers reveal the presence of disease or identify the subtype of disease. They can support differential diagnosis, confirm prognosis, or predict response to a pharmacological agent. 2) Monitoring biomarkers show the status of a disease with or without treatment and can act as surrogate end-points. Pharmacodynamic or response biomarkers provide information on the effect of a therapeutic intervention. 3) Predictive biomarkers predict human or environmental adverse effects and susceptibility to the effects of exposures. The magnitude and reproducibility of the challenge are critical when measuring biomarker precision, with precision in the chemical industry being quoted to within parts per million over the course of a day [54]. Levels of precision at this scale are rarely achieved in biological systems, particularly in clinical settings, where many unaccounted variables affect the outcome [55].

4. Conclusion

Appropriate quantities of ionizing radiation play a crucial role in medical radiotherapy, while radiotherapy techniques can affect the accuracy of clinical biomarkers. Precision in clinical biomarkers is critical for effective clinical application and cancer treatment. Ionizing radiation encompasses particles or electromagnetic waves capable of ionizing atoms or molecules in materials through which they pass, depositing energy in the process. Precise calculation and control of the dose deposited in organisms are essential. Radiotherapy has been studied for over a century, starting in the late 1800s with discoveries regarding x-rays and radioactivity. Radiotherapy is widely used in tumor treatment because appropriate doses can damage cellular structures and significantly hinder tumor cell proliferation. Contemporary techniques comprise 2-dimensional, 3-dimensional, intensity-modulated, image-guided, stereotactic, and volumetric-modulated radiotherapy, among others. Innovations such as stereotactic body radiotherapy, intensity-modulated radiation therapy, and proton therapy enable preciser tumour-targeted interventions with minimal damage to adjacent healthy tissues and exceptional control of cancerous cell growth. Clinical indicators or biomarkers fall into categories including molecular markers, genetic markers, and image markers, serving crucial roles in cancer diagnosis and monitoring. The response of tumour cell lines and associated damage have been investigated under various physical experiments, revealing complex processes following irradiation over time. The presence of estrogen or progesterone receptors affects radiation gene expression after both low and high doses of ionizing radiation. Variations in biomarker expression induced by radiotherapy stem from modifications in the physical and chemical environment at the measurement site, as well as changes in the biomarker structure. Consequently, values measured at identical time points can widely fluctuate, reducing the accuracy and sensitivity of biomarker analysis and leading to erroneous conclusions. The global radiotherapy market was valued at US\$5.5 billion in 2021 and is projected to reach US\$9.5 billion by 2031, growing at a compound annual growth rate of 5.9% during 2021–2031, demonstrating extensive adoption of radiotherapy techniques worldwide. Numerous case studies and clinical trials continue to evaluate biomarkers within radiotherapy contexts, and the development of novel radiotherapy technologies promises enhanced treatment quality and patient outcomes in the future.

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