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REVIEW ARTICLE

Radiotherapy: Its Dual Nature in Cancer Treatment in Terms of Immunotherapy and Low-Dose Radiation

Mustapha Mohammed Karagama[a], Fuaada Mohd. Siam[b]*, Norma Alias[b], Muhammad Mustapha[a], Dalal Yahya Alzahrani[c]

[a]Department of Mathematics, Faculty of Physical Sciences, University of Maiduguri, Borno State, Nigeria; [b]Department of Mathematical Sciences, Faculty of Science, Universiti Teknologi Malaysia, 81310 UTM Johor Bahru, Johor, Malaysia; [c]Department of Mathematics, Faculty of Science, Al Baha University, Al Bahah 65528, Saudi Arabia

Abstract This review paper critically analyses cancer treatment, examining the intricate aspects of radiotherapy (RT) and the promising prospects of virotherapy (VT) as a viable alternative strategy. We aim to explore the diverse effects of RT, providing a critical analysis of its dual nature as an effective method for cancer eradication and a potential cause of immunosuppression. The study delves into the complex relationship between immune responses and radiation effects, emphasizing the importance of meticulous treatment planning to optimize therapeutic outcomes. Additionally, it investigates the neurological and behavioural implications of low-dose radiation (LDR) on the brain, underscoring the need for comprehensive research to assess its long-term impact. The study presented VT as a promising and innovative approach to cancer treatment. The application of genetic engineering enables the use of viruses to precisely target and eliminate cancer cells while preserving the integrity of healthy tissue. Contemporary research and ongoing clinical trials have brought attention to the potential efficacy of VT as a standalone treatment or when used in conjunction with other therapeutic approaches. This paper provided an in-depth analysis of RT's dual nature in terms of immunotherapy (IT) and LDR, alongside the dynamic advancements in VT, this review highlights the potential of VT as a novel alternative and the pressing need for collaborative and multidisciplinary research. Hence, engaging in collaborative research within a multidisciplinary domain is highly recommended to develop a groundbreaking model that balance effective treatment with minimal adverse effects in the foreseeable future.

Keywords: Radiotherapy, cancer treatment, virotherapy, radiation effects, bystander cells.

***For correspondence:**
fuaada@utm.my

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Introduction

Cancer is a significant global public health issue and a leading cause of death worldwide [1, 2]. Over the years, various cancer treatment modalities, including chemotherapy, radiotherapy (RT), and immunotherapy (IT), have been developed to combat this life-threatening disease [2–5]. Among these, RT remains a cornerstone due to its efficacy in targeting and destroying cancer cells [2, 6]. However, RT is often associated with significant challenges, including irreversible damage to normal tissues and cells, such as bystander cells [2, 7-9]. These adverse effects underscore the need to develop more efficient RT models that mitigate its harmful consequences and address its limitations [2, 10–12].

The choice of cancer treatment often depends on factors such as the tumor type, location, the patient's overall health, and the type of radiation used [13–17]. Despite advances in RT and other therapies, the complex interplay between abnormal cancer cell growth and healthy tissue destruction remains a critical challenge [18, 19]. Tumor response to treatment also varies based on the cancer type and the patient's individual biology [19]. These factors highlight the pressing need for innovative cancer treatment strategies to minimize side effects and improve therapeutic outcomes.

RT can be broadly categorized based on the dosage of radiation delivered. Low-dose radiation (LDR) refers to doses typically below 100 mGy, which may elicit unique biological effects, such as immune modulation and bystander effects [20, 21]. In contrast, high-dose radiation (HDR) involves doses exceeding 1 Gy, which are conventionally used in cancer therapy to directly kill tumor cells but often lead to severe adverse effects on surrounding healthy tissues [20–22]. The distinction between LDR and HDR is critical to understanding RT's dual nature and its integration with IT, particularly in contexts such as brain cancer treatment.

This review focuses on the dual nature of RT in cancer treatment, particularly its integration with IT and the effects of LDR. The brain is emphasized as a case study due to its sensitivity to radiation and the unique challenges it presents in cancer therapy. Over two decades of RT use have revealed both its therapeutic potential and its significant adverse effects, necessitating evaluations of alternative treatment modalities to enhance efficacy while reducing harm.

The paper is organized as follows: Section Two provides a foundational understanding of RT in cancer treatment, including its definition and mechanisms of action. Section Three discusses cellular responses to radiation, exploring its impact on cancer cells, bystander cells, and immune cells. Section Four examines the types of radiation and their biological effects, with a specific focus on cellular exposure to ionizing radiation (IR). Section Five addresses the dual impacts of RT in cancer treatment, highlighting both its positive and negative effects. Section Six evaluates RT's integration with IT and LDR, using the brain as a model system for discussion. Section Seven explores the use of RT for specific cancer types and reviews emerging alternative approaches, such as virotherapy (VT). Finally, Section Eight concludes with a summary of key findings, emphasizing the importance of ongoing research and innovative therapies in advancing cancer treatment.

By critically analyzing RT's dual nature and its alternatives, this review aims to enhance understanding of current cancer therapies and their implications, paving the way for future advancements.

Fundamentals of RT in Cancer Treatment

Definition and Principles

This section summarizes the pertinent literature to enhance readers' understanding of the underlying mechanisms of cancer development. Cancer emerges due to dysfunction within cells, disrupting their normal functions and leading to uncontrolled cell division. This aberrant cell cycle perpetuates the proliferation of cancer cells. RT exploits this vulnerability by inducing DNA damage in rapidly dividing cells, making it a cornerstone of cancer treatment. The following discussions will delve into key concepts and findings from relevant research to critically review the topic.

Mechanisms of Radiation Interaction with Cells

Cells are the fundamental unit of life and the foundation for all living things. Each cell is an independent entity with a unique collection of structures and functions that enable it to perform its functions. Understanding cellular structure and function is crucial for elucidating how RT targets and interacts with cancer cells while sparing normal tissues [23–25]. We will discuss the structure, purpose, cell categories, and several types of cells as illustrated in Figure 1.

All cells have a fundamental structure that varies slightly based on their type and purpose. The essential parts of a cell include the cell membrane, a thin, pliable covering that encloses the cell and separates its internal environment from the outside world. It comprises a lipid bilayer and several proteins that regulate the entry and exit of substances [25, 26]. The term "cytoplasm" refers to the gel-like material that makes up a cell and contains a variety of organelles and chemicals. The nucleus serves as the cell's command center, controlling gene expression and housing genetic material (DNA). Similarly, organelles are specialized cell structures that perform specific tasks, such as mitochondria for energy production, the endoplasmic reticulum for protein synthesis, and the Golgi apparatus for sorting and packaging molecules [23–25]. These structures are critical targets for RT, particularly DNA, as IR induces DSBs that impair the survival of rapidly dividing cancer cells [27–30].

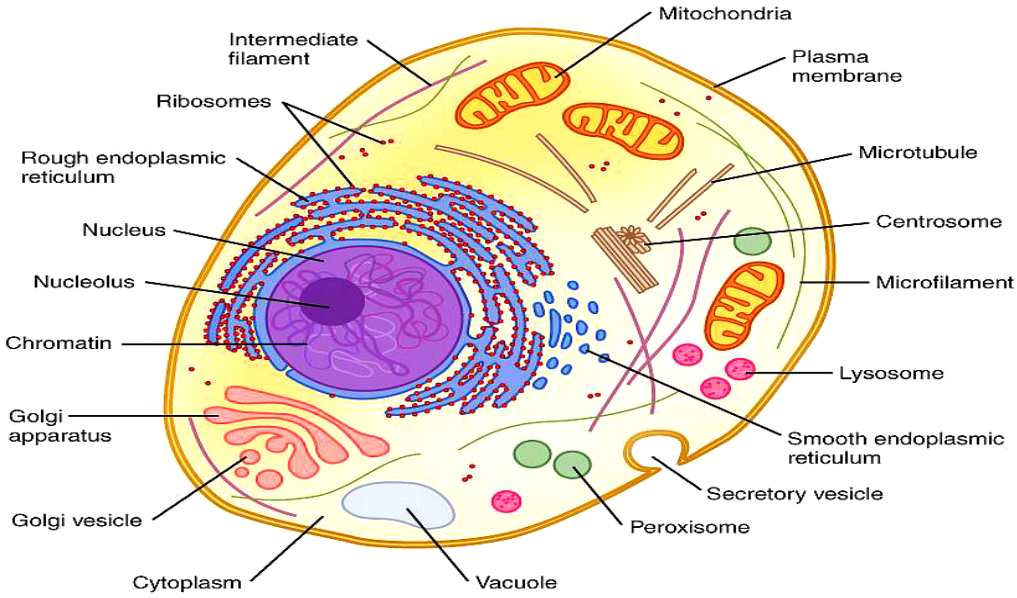

Figure 1. Cell Structure [31]

Two primary categories of cells exist, specifically prokaryotic cells and eukaryotic cells. Prokaryotic cells are generally smaller and less complex in structure than eukaryotic cells. The absence of a distinct nucleus and membrane-bound organelles characterizes prokaryotes. Prokaryotic cells are present in microorganisms classified under the domains of Bacteria and Archaea. In contrast, eukaryotic cells exhibit greater complexity and size compared to prokaryotic cells. Eukaryotic cells possess a distinct nucleus that contains genetic material (DNA) and multiple organelles enclosed by membranes, each performing specialized tasks. Eukaryotic cells constitute the cellular composition of all multicellular organisms, encompassing plants, animals, fungi, and protists. These distinctions are critical in understanding the selective targeting mechanisms of RT [23–25].

Different cells perform specific tasks depending on their type and location in the body. The generation of energy through processes like photosynthesis and cellular respiration is a key function of cells. Protein synthesis is another vital process, in which cells create proteins from deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), enabling numerous biological activities. Cellular communication refers to how cells use signaling mechanisms, such as hormones and neurotransmitters, to interact and regulate functions. Additionally, specialized cells, like muscle cells, can contract to facilitate movement [23–25]. RT impacts these processes differently in cancerous and healthy cells, with LDR potentially sparing normal tissues while HDR focuses on eradicating malignancies [32].

Cellular Responses to Radiation

Cancer cells

Globally, cancer remains the second leading cause of mortality, accounting for approximately 9.6 million deaths in 2018 according to the World Health Organization (WHO) [33]. Oncology, the field focused on cancer prevention, diagnosis, and treatment, plays a pivotal role in combating this life-threatening disease [34].

Cancer cells are aberrant cells that proliferate uncontrollably, often forming tumors through metastasis. This process enables cancer cells to invade neighboring tissues and spread to distant organs via the bloodstream or lymphatic system [35, 36]. Despite the variability among cancer types, several common characteristics define cancer cells:

(a) Lack of growth control: Cancer cells bypass normal regulatory mechanisms, avoiding apoptosis and allowing unchecked proliferation [35, 36].

(b) Ability to metastasize: Malignant cells detach from the primary tumor, migrate, and establish secondary tumors [35, 36].

Cancer development is influenced by genetic mutations in tumor suppressor genes or oncogenes and environmental factors such as carcinogen exposure, chronic inflammation, and viral infections. Additionally, cancer cells exhibit distinct metabolic adaptations, including the Warburg effect, enabling energy production in low-oxygen environments to support rapid proliferation. These cells also evade immune detection by altering surface proteins or suppressing immune responses, further complicating the treatment [37–39]. A pictorial representation of the cancer development is provided in Figure 2.

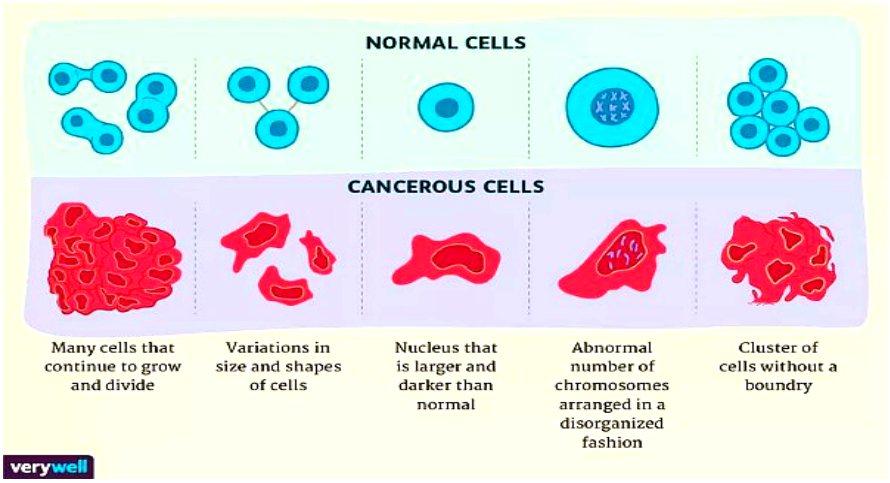

Figure 2. Normal cells vs cancer cells [40]

Bystander cells

While direct damage to DNA in irradiated cells is a major effect of IR, bystander cells are non-irradiated cells that receive signals from irradiated cells which exhibit biological changes. This phenomenon underscores the importance of intercellular communication in radiation-induced effects [41].

Studies using cytoplasmic hybrids (cybrids) revealed that mitochondria play a key role in bystander effects. DNA damage was assessed in cybrid cell lines irradiated at low (0.2 Gy) and high (2.0 Gy) doses. Wild-type mitochondria (Cy143Bwt) and mutant mitochondria (Cy143Bmut) demonstrated significant DNA damage, while cells without mitochondria (143B-Rho0) showed no such effects. This suggests that mitochondria mediate bystander responses to radiation [42].

Furthermore, microbeam irradiators, which allow precise delivery of radiation to specific subcellular regions, have advanced research on bystander effects. These studies have revealed that molecular signaling mechanisms, such as those involving DNA damage responses, mediate non-targeted effects of IR. This knowledge has potential applications in precision RT and radiation protection strategies [43–45].

Immune cells

Immune cells, integral to the body's defense system, are categorized by their roles, as shown in Figure 3. They include:

(a) T lymphocytes (or T cells): Including helper, cytotoxic, and regulatory subtypes, these cells are crucial for adaptive immunity.
(b) B lymphocytes (B cells): Responsible for antibody production and immunological memory
(c) Natural killer cells (NK cells): Innate immune cells that identify and kill infected or abnormal cells.
(d) Dendritic cells (DC): Antigen-presenting cells that activate T cells.
(e) Macrophages: Phagocytes that digest foreign material and present antigens to T cells.
(f) Neutrophils: First responders to infection.
(g) Mast cells: Mediators of allergic reactions [46–48].

RT interacts with immune cells in complex ways. It can enhance anti-tumor immunity by activating immune cells or suppress immunity at higher doses. Combining RT with immunotherapy holds promise for improving treatment outcomes.

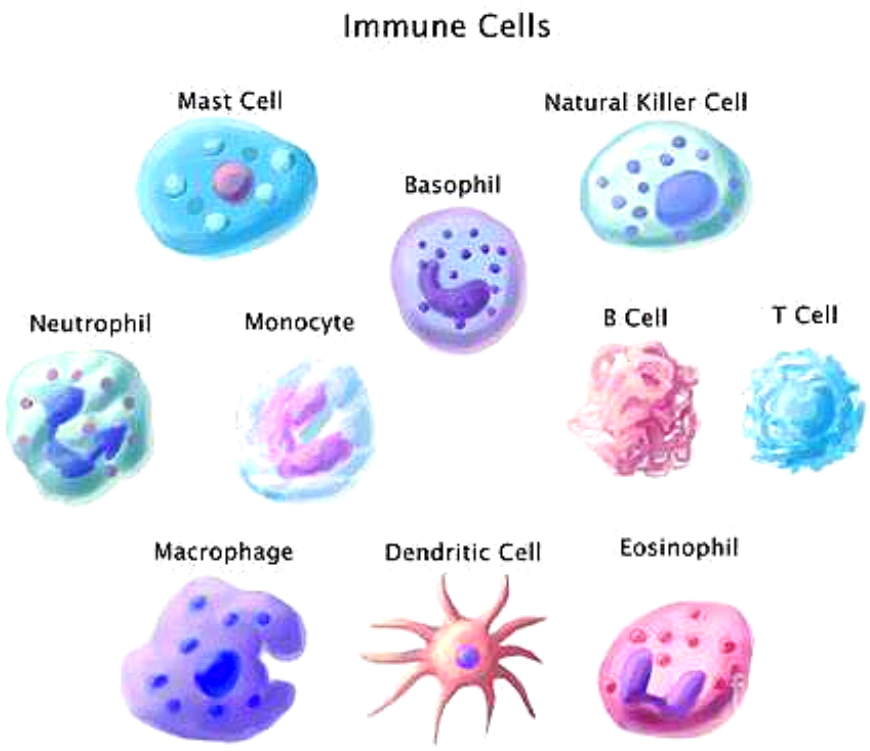

Figure 3. Immune cells [49]

Types of Radiation and Their Biological Impacts

Radiation Types

Radiation, the emission of energy as waves or particles, is categorized into IR and non-ionizing radiation (NIR). IR has sufficient energy to ionize atoms, whereas NIR, including radio waves and visible light, lacks this capacity and generally has minimal health effects [44, 50–53].

IR is further classified by its energy transfer characteristics:
1) Low linear energy transfer (LET): Includes X-rays, gamma rays, beta particles, and electrons.
2) High LET: Includes alpha particles and neutrons, causing denser ionization tracks and more severe biological damage [51–53].

Radiation dose, measured in gray (Gy), refers to the energy absorbed by tissues. LDR involves minimal exposure, while HDR represents elevated exposure levels. Both LDR and HDR can involve low or high LET radiation, with biological impacts dependent on the interplay of dose and LET [54, 55].

Radiobiological Responses to Ionizing Radiation

The effects of IR range from beneficial, such as RT's therapeutic role, to harmful, including Acute Radiation Syndrome (ARS) and chronic health risks like cancer and cardiovascular diseases [44, 50]. For instance, radiosensitive mice exposed to LDR showed increased leukemia risk due to mutations involving the Sfpi1 (spleen focus forming virus (SFFV) proviral integration oncogene 1) gene [56]. Similarly, combining high and low RT doses in hybrid strategies has shown promise but requires further optimization [57–60].

DNA damage, particularly DSBs, underpins many IR-induced effects. Cells repair DSBs via homologous recombination (HR) or non-homologous end joining (NHEJ) [43, 61–64]. Chromatin structure and histone modifications significantly influence repair efficiency [65]. Variants like H2A.X play a pivotal role in DNA damage responses and genomic stability [66].

Emerging Insights

Advancements in understanding DNA repair mechanisms, such as RNA's role in damage response and chromatin relaxation through histone acetylation, are informing new therapeutic approaches [65]. Studies on cellular radiosensitivity have highlighted differences among blood cell populations, guiding efforts to minimize RT's side effects while maximizing its efficacy [67].

Dual Impacts of RT on Cancer Treatment

Considering the dual nature of RT, it is essential to evaluate both its evident advantages and hidden complexities. This section delves into this duality, drawing insights primarily from a critical review of immunotherapy (IT) and low-dose radiation (LDR) conducted over two years (2022-2023). Foundational studies outside this range are included selectively to provide essential context or validate recent findings. The section outlines key mechanisms, methodologies, and limitations encountered during the evaluation process.

Positive Impacts of RT

Mechanisms of Action and Treatment Efficacy

RT has been demonstrated to enhance the immune response against cancers, leading to the suppression of both irradiated tumors and distant metastases, as depicted in Figure 4. The interaction begins with IR inducing the release of double-stranded DNA (dsDNA) from the nucleus and increasing the permeability of the mitochondrial outer membrane. Consequently, mitochondrial DNA (mtDNA) becomes cytosolic and detectable [68–71]. This activates the cGAS-STING pathway (cyclic GMP-AMP synthase - Stimulator of Interferon Genes), which promotes the synthesis of type I interferons (IFNs I) [68, 72,73]. These IFNs coordinate a sequence of immune responses, including dendritic cell (DC) activation, which primes T lymphocytes, thereby playing a pivotal role in regulating tumor growth [68, 74, 75].

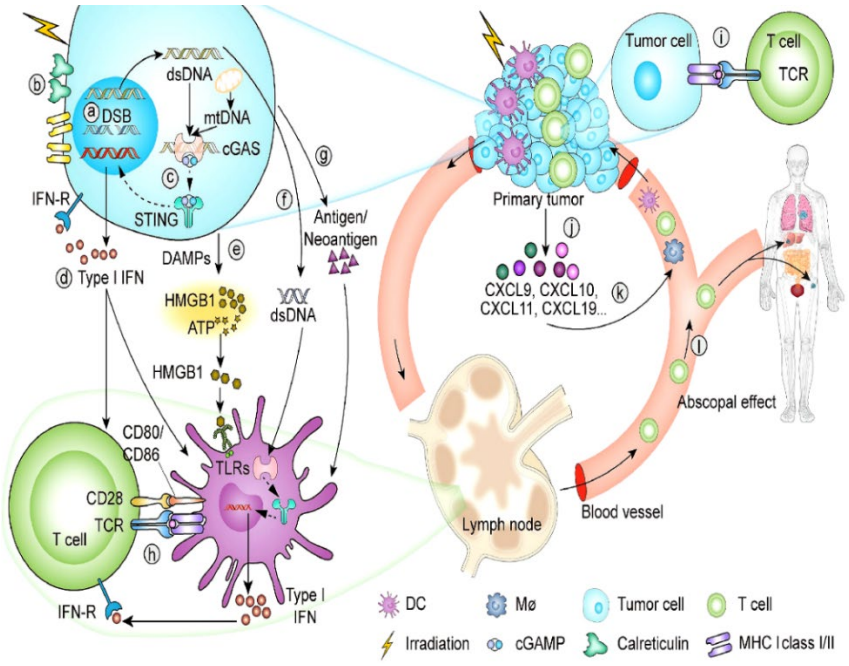

Figure 4. RT triggers an immune response against tumours through multiple mechanisms [68]

Additional mechanisms, such as enhanced expression of MHC-I molecules in tumor cells and the generation of tumor-associated antigens (TAAs), broaden the immune system's ability to identify and target cancer cells. Moreover, RT modulates the tumor microenvironment by releasing proinflammatory chemokines, including CXCL9, CXCL10, and CXCL11, which attract immune cells to the site [68, 76–78].

Dendritic cells transport tumor debris to lymph nodes, presenting antigens and activating diverse T-cell receptor (TCR) variants. This process augments immune response diversity and amplifies anti-tumor immunity [68, 79, 80]. The amalgamation of RT and IT can further enhance these immune responses, triggering systemic cancer regression and the abscopal effect, a phenomenon where localized RT also benefits non-irradiated metastases [68, 81].

Positive Impacts of LDR

LDR has been shown to elicit protective responses [82, 83], activating natural repair mechanisms and immune reactions [68]. Evidence suggests LDR promotes neurogenesis in the hippocampus [84, 85], improves antioxidant defenses [86], and supports recovery in diabetic rats [87]. Studies, such as [85, 88, 89], have provided valuable insights into LDR's potential therapeutic benefits in neurodegenerative conditions, highlighting its ability to improve motor, cognitive, and sensory functions. However, these findings are limited by small sample sizes and late-stage treatment scenarios.

Successful Local Cancer Control and Palliative Benefits

RT is a cornerstone in cancer therapy, employed for curative and palliative purposes. Its immunogenic potential augments local and systemic immune responses, contributing to effective tumor eradication and symptom relief [68]. For palliative care, RT alleviates pain, improves quality of life, and may synergize with LDR to offer benefits in neurodegenerative diseases like Alzheimer's and Parkinson's [88–90].

The effects of LDR on neuronal cells, as depicted in Figure 5, and its consequences during different developmental periods, including gestation, neonatal stage, and adulthood, have been consolidated and displayed in Tables 1 to 3 [88].

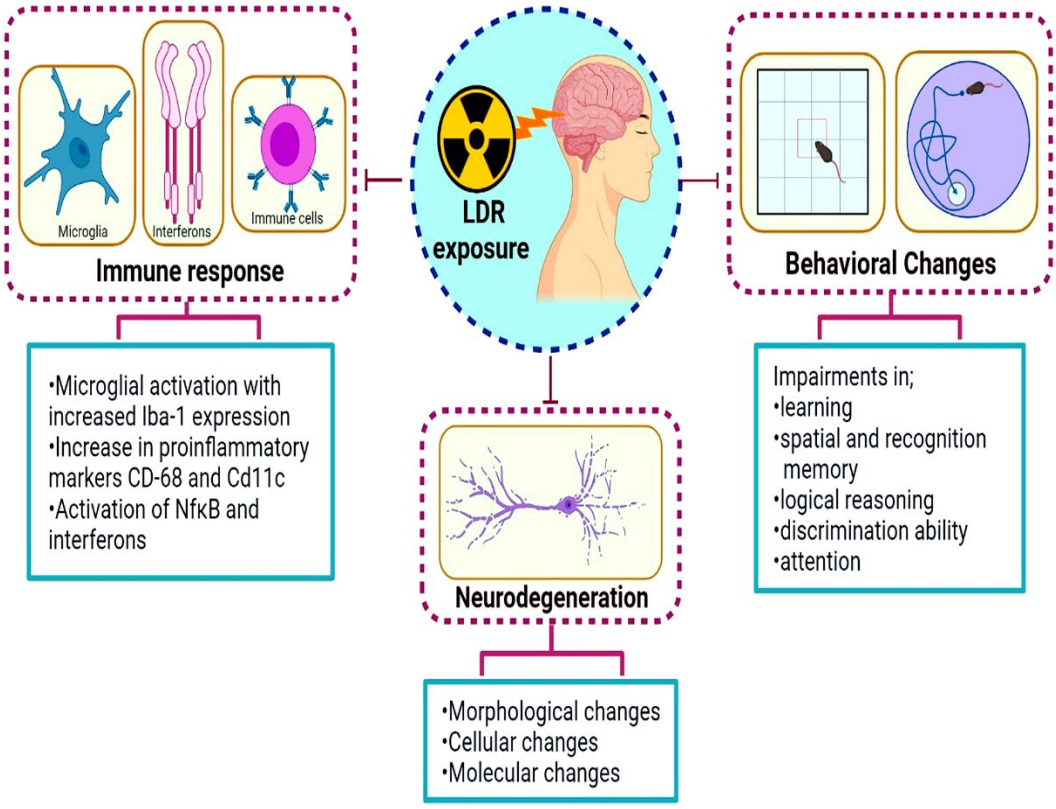

Figure 5. The multiple impacts of LDR exposure on the brain include behavioural, immunomodulatory, and neuronal effects [88]

The purpose of these overviews is to enhance our comprehension of the complex correlation between LDR and its various effects on human health regarding RT.

Negative Impacts of RT

Adverse Effects and Complications

The process of immunogenic radiation induces the accumulation of dsDNA within cancer cells, thereby triggering the amplification of the cGAS/STING signaling pathway. This process enhances the transcription rate for genes encoding IFNs I (IFN-α and IFN-β) [68]. Nevertheless, it is crucial to acknowledge that the activation of interferon (IFN) signaling pathways can result in the development of resistance to treatment [91]. Repeated exposure of cancer cells to irradiation results in the sustained activation of IFNs I and the subsequent upregulation of IFNs-stimulated genes. These molecular alterations are crucial in conferring radiation resistance and promoting cancer cell spread to distant sites through diverse inhibitory mechanisms [27, 92].

Additionally, the increased expression of programmed death-ligand 1 (PD-L1) on neoplastic cells as a result of IFN-γ (type II interferons or IFNs II) and IFNs I further compounds the problem by depleting T-cells and compromising the body's ability to mount an effective immune response against tumors [68, 93, 94]. Additionally, it has been observed that IFNs I and IFNs II play a role in enhancing Indoleamine 2,3-dioxygenase (IDO) expression, which is known to have immunosuppressive properties [68, 95].

The activation of STING signaling not only leads to the recruitment of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) but also results in reduced tumor immunogenicity [68, 96–98]. Local irradiation is associated with the upregulation of (C-C motif chemokine ligand) CCL2 and CCL5, which subsequently attract Tregs and monocytes, promoting an immunosuppressive milieu [68, 99, 100]. Furthermore, regulatory T cells (Tregs) activated by monocytes stimulated with TNF-α reduce the effectiveness of radiation and lead to immune resistance against tumors [68, 99]. Tregs also contribute to worsening MDSC immunosuppression and inhibit effector T cells through the release of interleukin-10 (IL-10) and transforming growth factor beta (TGF-β) [68, 101, 102].

Lymphopenia and Immune Suppression

Lymphopenia is a common consequence of RT, as radiation affects the bone marrow located within the irradiated area [68, 103]. Even minimal levels of radiation can temporarily eliminate bone marrow, while moderate exposure may require years for active hematopoiesis to fully recover. In instances of high radiation exposure, irreversible harm can occur [68,103]. Myelosuppression manifests as blood cell depletion and lymphopenia, as many blood cells have a relatively short lifespan [68, 104, 105]. Additionally, IR has a detrimental impact on peripheral blood mononuclear cells, contributing to immune suppression [68, 106]. Regular exposure to traditional fractional radiation significantly reduces the migration of immune effector cells [68].

According to a study, the impact of a single dose of 2Gy of radiation on blood cells is approximately 0.5Gy (25%) [68, 107]. This proportion increases significantly to 92.2% (55.32Gy) when a regular 2Gy × 30 conventional radiation fraction is administered for brain cancers [68,108]. Leukopenia and immune suppression are observed when blood cells are exposed to IR. Furthermore, irradiation of lymphatic organs, such as elective nodal irradiation, induces lymphopenia. Naive T cells may undergo p53-mediated apoptosis due to low-dose radiation (LDR) of lymphoid tissue [68, 109, 110]. The direct irradiation of draining lymph nodes (DLNs) leads to lymphatic toxicity and decreases the number of viable clusters of differentiation 45 (CD45+) cells [68, 111]. Figure 6 illustrates an overview of the advert effects of RT.

The irradiation of cancer-associated DLNs as an elective measure has been shown to negatively affect adaptive immune responses, primarily through chemokine production alterations and impaired CD8+ T-cell mobility [68, 111]. Additionally, galectin-1 (Gal-1) released from cancer cells after RT stimulates T-cell apoptosis and contributes to lymphopenia [68, 112].

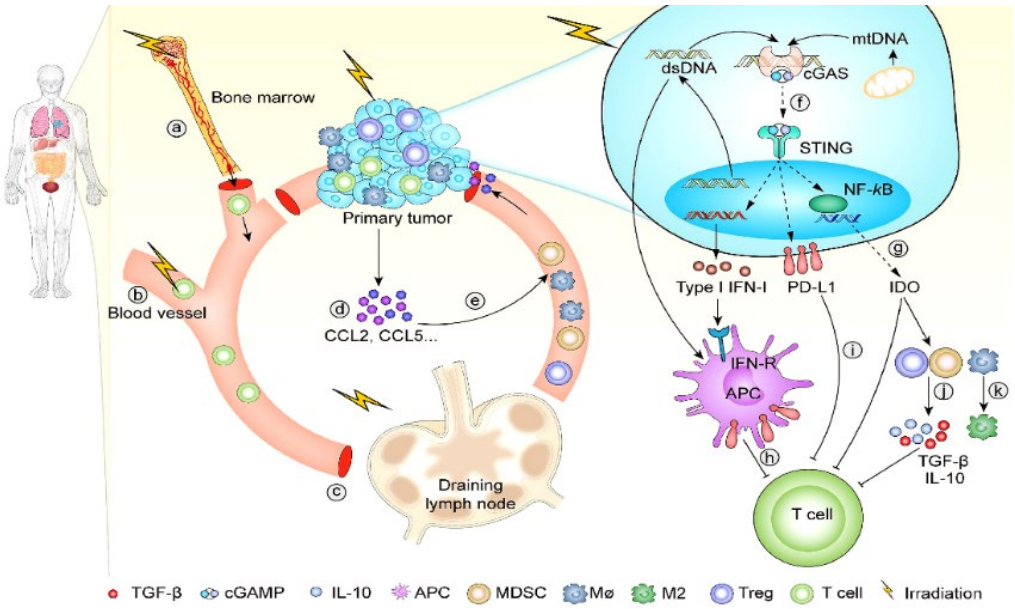

Figure 6. The administration of RT induces lymphopenia and immunosuppression [68]

LDR and Behavioral Impacts

Recent research highlights the dual effects of LDR on behavior. A study revealed that mice exposed to certain conditions demonstrated delayed yet beneficial effects on exploratory behavior and sensorimotor recruitment [88, 113, 114]. This finding is particularly significant, given the use of animal models, such as rats and drosophila, to study brain changes caused by LDR exposure [88, 115].

However, LDR exposure has also been associated with adverse behavioral effects. For example, pregnant rats exposed to doses of the radiological tracer 3H2O (46 mGy, 92 mGy, and 273 mGy) exhibited offspring with impaired learning responses in passive avoidance tests and reduced conditioned reflex establishment [88, 116]. Similarly, a study on pregnant rats exposed to LDR (10-100 mGy) reported decreases in both cingulum bundle size and brain weight in the offsprings [116]. Another study demonstrated a dose-response relationship in Swedish military personnel exposed to LDR during treatment for cutaneous hemangioma, resulting in impaired learning, logical reasoning, and educational achievement [88, 117].

Behavioral changes are often attributed to intricate signaling pathways involving genes and proteins critical to neuronal survival [88]. LDR modulates antioxidant systems, cellular enzyme levels, and other key chemicals essential for neuron survival, leading to either beneficial or detrimental outcomes [88,118]. For example, neural cultures from fetal mice exposed to LDR of 100 mGy exhibited observable morphological abnormalities within 24 hours [88, 119, 120].

LDR also influences genes related to oxidative stress, neuroinflammation, synaptic plasticity, and the connectome. These effects have not been observed in high-dose radiation exposure [88, 121]. A study examining human embryonic stem cells exposed to computed tomography (CT) doses of 15 mGy reported decreased Nestin expression, a marker for neural progenitor cells, suggesting reduced neurogenesis [88, 122].

Moreover, LDR exposure alters tau protein expression in the cerebral cortex and activates microglia, contributing to neuroinflammation [88,123]. It has also been shown to activate the NF-kB signaling pathway, which regulates transcription of superoxide dismutase 2 (SOD2), a key antioxidant enzyme [88, 124]. Mitochondrial activity is also enhanced by LDR, potentially mitigating oxidative stress-related damage [88, 125–127].

Lastly, LDR significantly impacts genes involved in DNA repair, cell cycle regulation, synaptic signaling, and redox pathways. These genetic alterations contribute to the observed neurological changes following LDR exposure [88, 128, 129].

Radiotherapy in the Context of Immunotherapy and Low-Dose Radiation

RT necessitates careful dose adjustments and treatment planning to enhance immune activation while minimizing immune suppression [68, 130]. Protecting lymphocytes is critical for inhibiting both local and distant tumor growth [5, 68]. A recommended strategy involves minimizing radiation exposure to bone marrow and circulating blood. This approach requires precise determination of target volumes and irradiation dosages. Furthermore, inhibiting T cells in DLNs, which are essential for antigen presentation by DCs and T-cell activation, could compromise the adaptive anti-tumor immune response [68, 131]. Therefore, a cautious approach to DLN irradiation is advised [68].

RT often elicits significant immunomodulatory effects, leading to scenarios where specific RT regimens may not align well with IT. To optimize the synergy between RT and IT, an in-depth understanding of the complex immunological pathways influenced by RT is crucial [68]. Although the plausibility of this approach is supported by preliminary evidence, further conclusive confirmation is required to establish its efficacy.

Determining the optimal sequence for administering RT and IT necessitates considering individual variations, tumor-specific traits, radiation characteristics, and IT-specific variables [68]. The complexity of these interactions poses challenges in analyzing all contributing factors. However, a personalized sequence tailored to an individual's profile has the potential to improve prognostic outcomes significantly [68]. The intricate interplay between RT and IT underscores the need for ongoing research to identify the most effective strategies.

However, emerging research is essential to unravel the heterogeneous effects of LDR on the brain. Insufficient public awareness about these effects could inadvertently encourage careless use of radiological procedures. Investigating the link between the prevalence of neurodegenerative disorders and radiological practices is paramount for enhancing cerebral protection and improving the quality of life [88].

The challenges of LDR research are amplified by inconsistent and imprecise outcomes for identical doses and a lack of epidemiological support. Variability among individuals and experimental settings exacerbates these limitations, hindering reproducibility and reliability [88]. These inconsistencies raise concerns about extrapolating findings from animal models to humans. Moreover, a critical aspect of LDR research involves administering a 100 mGy dose, which has been associated with potential adverse effects [88].

In summary, the intricate interactions between immunogenic radiation, cancer cells, the immune system, and gene expression collectively contribute to treatment resistance and complex immune responses. Furthermore, the behavioral and neurological effects of LDR emphasize the multifaceted relationship between radiation exposure and biological outcomes (see Table 1). A deeper understanding of these mechanisms is essential to enhance therapeutic approaches while minimizing adverse consequences.

Call to Action

This analysis unequivocally demonstrates the dichotomous nature of RT, characterized by its therapeutic potential and accompanying challenges. This realization underscores the urgency for a paradigm shift in exploring alternative cancer treatment strategies. While RT offers promise, its inherent difficulties and adverse consequences demand careful consideration.

Researchers and medical practitioners are encouraged to explore innovative cancer treatments that mitigate the negative effects of RT. Further research is imperative to uncover novel approaches capable of addressing RT’s challenges effectively. With a focused and systemic approach, the goal is to propose comprehensive cancer treatment options, highlighting the effects of LDR, especially on the brain as illustrated in Figure 7. This approach seeks to mitigate the adverse effects often associated with conventional techniques.

Sustained commitment to medical research is crucial for transforming cancer therapy and improving patient outcomes. While the challenges are substantial, the potential benefits are transformative. Advancing towards safer and more effective cancer treatments is a shared responsibility, demanding collective efforts.

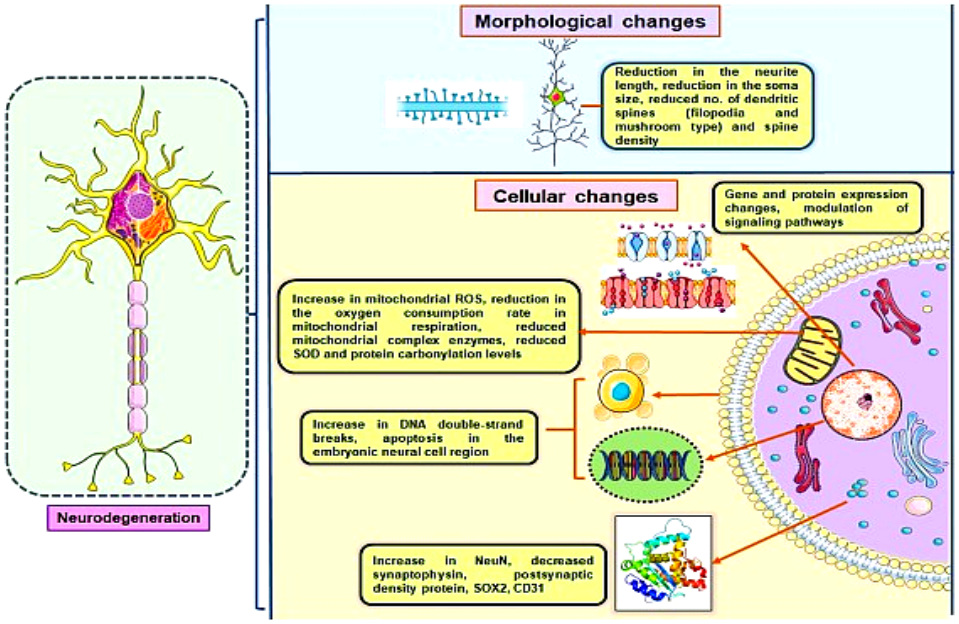

Figure 7. Impacts of LDR [88]

Table 1. An Overview of IT and LDR

S/N	Year	Title	Study type	Aim	Finding(s)	Remark(s)	Refs
1.	2022	Radiotherapy: Brightness and darkness in the era of immunotherapy	Research article on IT	To explore the synergy between RT and IT and identify optimal strategies for combined therapy.	RT is dual in nature, as it can either suppress or enhance immune responses based on dose and schedule. Hypofractionated RT combined with IT shows greater promise in improving therapeutic outcomes. Reducing radiation exposure and leveraging advanced RT technologies can optimise results.	The immunomodulatory effects of RT must be considered when combined with IT. Further experimental and clinical research is essential to enhance efficacy and develop new modalities.	[68].
2.	2022	Effects of low dose ionising radiation on the brain- a functional, cellular, and molecular perspective	Review article on the effects of LDR on the brain.	To provide insights into LDR's impacts on functional, cellular, and molecular levels, exploring its risks and benefits.	LDR has minimal effects on neonatal mice at low LET doses (20–100 mGy). Despite potential benefits for neurodegenerative disorders, LDR can cause adverse effects like reduced brain weight and pyramidal cell count in rats. Diverse neurological impacts have been documented in exposed individuals, raising debates about radiation hormesis.	A reassessment of LDR dosage and exposure frequency is necessary. Most studies use a 100 mGy threshold, which may contribute to adverse effects. Doses below 100 mGy should be prioritised for safer applications.	[88].

S/N	Year	Title	Study type	Aim	Finding(s)	Remark(s)	Refs
3.	2023	Low-dose radiotherapy effects the progression of anti-tumor response	Research article on LDR	To explore how LDR influences the immune response and tumor microenvironment.	LDR enhances immune cell activity, shifts immune responses towards anti-tumor phenotypes, and modulates the tumor microenvironment to increase T cell infiltration.	LDR shows potential in reprogramming the tumor microenvironment, but dose optimization is required to minimize risks.	[83].
4.	2022	Protective effect of low-dose radiation on doxorubicin-induced brain injury in mice	Experimental study on LDR	To investigate the protective effects of LDR on brain injury induced by doxorubicin.	LDR mitigates oxidative stress, reduces apoptosis, and improves mitochondrial function, leading to protective effects against cognitive decline.	LDR could serve as a non-invasive therapeutic strategy to address neurotoxicity from chemotherapy.	[132].
5.	2023	Recent Advances in Molecular Mechanisms of Cancer Immunotherapy	Review article on IT	To discuss recent advancements in the molecular mechanisms of cancer immunotherapy.	Highlights include enhanced understanding of the cancer immunity cycle, immune checkpoint inhibitors, and genetically modified immune cells. The integration of cytokine therapies and T-cell engineering has revolutionized cancer treatment.	Significant progress in understanding tumor immunobiology opens new therapeutic opportunities, but challenges remain in patient-specific responses.	[93].
6.	2023	Antigen discovery for the development of cancer immunotherapy	Research article on IT	To explore how mass spectrometry and other omics technologies aid in identifying tumor antigens for immunotherapy.	Mass spectrometry-based immunopeptidomics enables precise identification of tumor-specific antigens (TSAs) and tumor-associated antigens (TAAs), advancing cancer vaccines and adoptive T-cell therapies.	The integration of antigen discovery technologies with immunotherapies offers potential for personalized medicine, though challenges in target validation persist.	[76].
7.	2022	Autophagy, ferroptosis, pyroptosis, and necroptosis in tumor immunotherapy	Review article on IT	To summarize the role of non-apoptotic regulated cell deaths (RCDs) in enhancing immunotherapy efficacy.	RCDs such as ferroptosis and pyroptosis enhance antitumor immune responses and could convert immune 'cold' tumors into 'hot' tumors, making them more responsive to immunotherapy.	Combining IT with RCD-targeting therapies may overcome resistance in certain tumor types.	[75].
8.	2023	Low-dose exposure to malathion and radiation culminates in the dysregulation of multiple neuronal processes	Research article on LDR	To investigate the combined effects of LDR and malathion on neuronal processes and potential neurodegenerative pathways.	Combined exposure to malathion and LDR led to increased oxidative stress, decreased neuronal viability, and significant changes in dendritic morphology. Synergistic neurotoxic effects were observed, including altered gene expression in pathways related to neurodegeneration.	The study highlights the compounded risks of combined exposures to xenobiotics and radiation, emphasizing the need for revised safety thresholds.	[118].

S/N	Year	Title	Study type	Aim	Finding(s)	Remark(s)	Refs
9.	2023	Low-Dose Non-Targeted Effects and Mitochondrial Control	Review article on LDR	To explore the role of mitochondrial signaling in NTEs and LDR induced responses.	LDR triggers mitochondrial-mediated NTEs, such as bystander effects, adaptive responses, and genomic instability. It also induces oxidative stress and signaling pathways that impact DNA repair, immune responses, and tumor suppression.	The involvement of mitochondria in radiation-induced NTEs highlights their importance in therapeutic strategies, with implications for improving RT outcomes and understanding LDR risks.	[82].
10.	2023	Radiotherapy and Immunotherapy	Research article on IT	To analyze the interplay between RT and IT, highlighting their mutual impact on cancer treatment efficacy.	Combination of RT and IT, particularly immune checkpoint inhibitors, enhances antitumor immune responses. Clinical trials demonstrate improved progression-free survival (PFS) and overall survival (OS) in NSCLC, melanoma, and cervical cancer patients. RT triggers the release of tumor-associated antigens, stimulating adaptive immunity.	Future studies should explore optimal sequencing, dosing, and combinations of RT and IT to maximize therapeutic efficacy.	[130].

Broader Discussions

RT for Specific Cancer Types

This section provides an analysis of successful cancer treatments using RT while addressing the challenges and limitations encountered during treatment. Table 2 outlines selected studies examining the application of RT for various cancer types, methodologies employed, and associated challenges.

Table 2. RT treatment of some cancer types

S/N	Year	Treatment type	Method	Cancer type	Study type	Sample size	Dose-volume	Overall survival	Median follow-up period	Challenges	Refs
1.	2023	RT	Cardiac magnetic resonance (CMR) and Left ventricle (LV) Dose-volume histogram (DVH)	Esophageal cancer	Prospective	23 patients	> 30Gy	Low	82.1 months	Adverse cardiac effects caused by RT were observed. LV V45 is linked to RT-induced myocardial damage and subsequent cardiac incidents. Magnetic resonance imaging (MRI) revealed heart damage for six months post-chemoradiotherapy (CRT), increasing the likelihood of cardiac complications.	[133].

S/N	Year	Treatment type	Method	Cancer type	Study type	Sample size	Dose-volume	Overall survival	Median follow-up period	Challenges	Refs
2.	2023	RT	Central shielding (CS)-Intensity-modulated radiotherapy (IMRT)	Uterine cervical cancer	Retrospective	54 patients	50.4Gy in 28 fractions	82%	56 months	Significant efficacy and toxicity profiles for CS-IMRT. The study was limited by the infrequent use of PET-CT and CT imaging. Prospective trials are recommended for a more comprehensive assessment of efficacy and toxicity.	[134]
3.	2023	RT	External beam radiotherapy (EBRT) and LDR brachytherapy	Head and Neck	Experimental	20 rabbits	20-50Gy	75%	NA	This study was conducted on animal subjects and has not been extended to humans. Higher radiation exposure levels caused statistically significant increases in apoptosis across groups.	[135]
4.	2023	RT	IMRT, Volume modulated arc therapy (VMAT) and Helical tomotherapy (HT)	Early stage Left-sided breast cancer after BCS	Clinical	35 patients	50Gy	NA	NA	The study failed to account for respiratory motion's impact on the entire breast. VMAT plans showed slightly elevated values for low-dose volume metrics (V2.5 and V5 Gy), mean dose, and secondary cancer complication probability (SCCP) compared to IMRT. HT plans exhibited higher SCCP and EAR values.	[136]

The studies summarised in Table 2 highlight both the advancements in RT techniques and the persistent challenges. For esophageal cancer, cardiac damage is a significant concern when using RT due to its proximity to the heart. Technologies like CMR imaging and DVH offer valuable insights into minimizing damage but require broader clinical trials to validate their effectiveness [133].

In uterine cervical cancer treatment, combining CS with IMRT showed promising results in improving overall survival rates. However, the lack of standardised imaging protocols, such as PET-CT, limits its broader application. Future prospective trials can address these limitations and provide a more nuanced understanding of its efficacy and toxicity [134].

For head and neck cancers, experimental studies utilizing EBRT and LDR brachytherapy in animal models suggest potential benefits, particularly in inducing apoptosis. However, translating these findings to human populations remains a critical gap that must be addressed through clinical trials [135].

In the treatment of early-stage left-sided breast cancer post-breast-conserving surgery (BCS), advanced techniques like IMRT, VMAT, and HT present challenges in terms of accounting for respiratory motion. Additionally, variations in secondary cancer complication probabilities (SCCP) and excess absolute risks (EAR) across treatment modalities highlight the need for tailored approaches based on individual patient profiles [136].

Continued research is vital to refine RT methodologies and integrate innovative technologies to mitigate associated challenges. The interplay between RT doses, treatment precision, and patient-specific factors underscores the necessity for personalised treatment strategies. Expanding clinical trials across diverse cancer types will bridge the gap between experimental findings and real-world applications, ensuring improved outcomes for patients.

Alternative Approaches to RT

Definition and Principles of Virotherapy

Virotherapy (VT) refers to the therapeutic application of viruses to treat various diseases, including cancer. It encompasses several modalities such as oncolytic virotherapy (OVT), where viruses are specifically designed to target and destroy cancer cells, gene therapy using viruses as vectors for delivering therapeutic genes, and vaccine therapy where viruses stimulate immune responses [137-139].

At its core, OVT leverages genetically modified viruses to selectively infect, replicate within, and ultimately destroy cancer cells. This process exploits the innate replication machinery of viruses, wherein infected cancer cells are lysed, releasing new viral particles that propagate the infection to adjacent tumour cells. This cycle continues until the tumour is eradicated. Simultaneously, the lysis of cancer cells releases tumour-associated antigens (TAAs), which stimulate the immune system, enhancing its ability to identify and attack residual cancer cells [140–142].

The principle underlying VT is rooted in exploiting the differences between healthy and cancerous cells. Cancer cells often exhibit dysfunctional antiviral responses, making them more susceptible to viral infections. Genetically engineered viruses are designed to enhance this susceptibility while ensuring minimal off-target effects on healthy tissues [140, 141].

Applications and Potential of Virotherapy

Virotherapy has emerged as a groundbreaking approach in cancer treatment, offering a dual benefit: direct destruction of tumour cells and activation of the immune system. Modern advancements in genetic engineering have enabled the precise tailoring of viral genomes, improving tumour specificity and therapeutic efficacy [140, 143]. Key applications and potential of VT include:

- Cancer Cell Targeting and Destruction: Genetically modified viruses selectively target tumour cells, sparing healthy tissues. Upon infection, the viruses replicate within cancer cells, leading to their destruction and halting tumour progression [140, 144].
- Immune Activation: The release of TAAs during the viral lysis of tumour cells triggers robust immune responses. This immunogenic cell death attracts dendritic cells and T cells, enhancing systemic anti-tumour immunity [140, 142].
- Combination Therapies: VT can be integrated with traditional treatments like radiotherapy (RT), chemotherapy, and immunotherapy (IT). For example, combining OVT with RT can amplify tumour destruction while simultaneously mitigating immune suppression [137, 145–147].

Effects and Insights from Previous Studies

The potential of VT has been demonstrated in various preclinical and clinical studies:

- Enhanced Selectivity: Studies have shown that viruses engineered to express tumour-specific promoters significantly reduce off-target effects. For instance, viruses modified to replicate only in hypoxic tumour environments ensure precise targeting [144, 148].
- Immune Evasion Challenges: Early applications of spontaneous or wild-type viruses faced limitations, such as rapid clearance by the immune system. Genetically engineered viruses now incorporate strategies to evade immune detection, enhancing their persistence and efficacy [140, 142].
- Safety Improvements: Advances in molecular virology have addressed safety concerns by eliminating the risk of viral replication in healthy tissues. This has been achieved by introducing genetic safeguards that restrict viral activity to cancer cells [144, 148].
- Promising Clinical Results: In recent trials, oncolytic viruses such as talimogene laherparepvec (T-VEC) have demonstrated efficacy in melanoma patients, leading to tumour regression and prolonged survival [141, 145, 149, 150]. Figure 8 shows the generation of progress made in OVT.

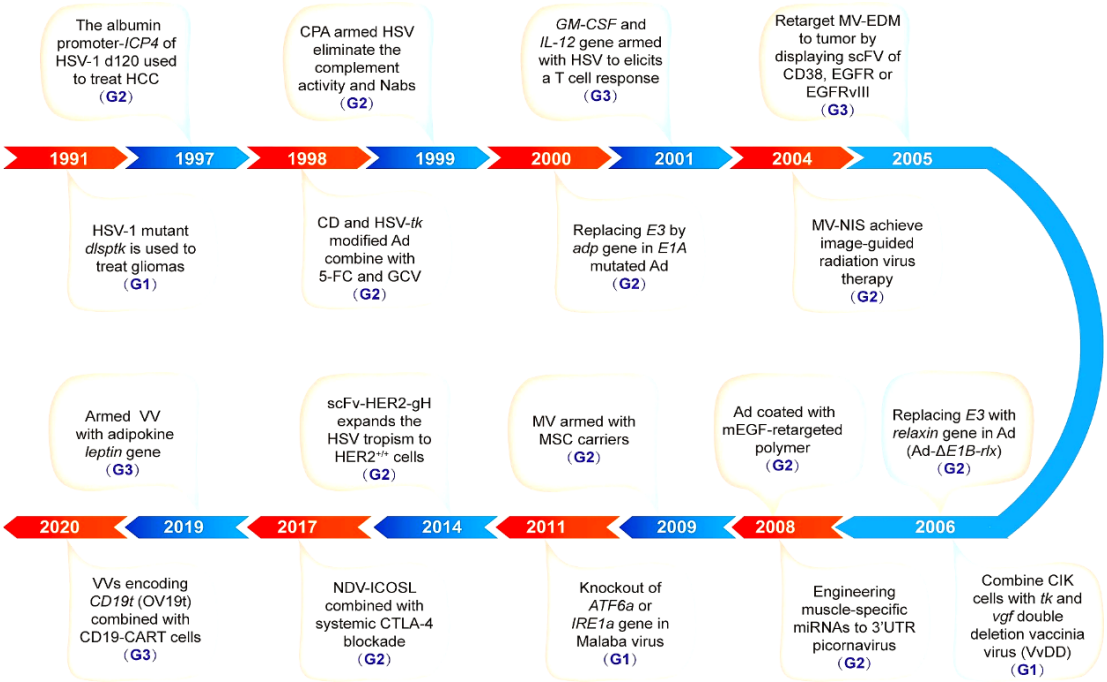

Figure 8. A chronological account of significant milestones in the evolutionary progression of OVT [148]

Challenges and Future Directions

Despite its promise, VT faces several challenges that require further exploration:

- Immune Clearance: The body's immune system often identifies and eliminates therapeutic viruses before they reach the tumour site, reducing efficacy [140].
- Delivery Mechanisms: Developing effective delivery systems to ensure viral particles reach the target without degradation is a critical area of research [151].
- Resistance Development: As with other therapies, tumours may develop resistance to VT, necessitating combination strategies or second-line treatments [152].

The future of VT lies in integrating it with other modalities like RT and IT, refining genetic modifications, and addressing delivery challenges. The insights gained from ongoing studies continue to shape VT as a promising alternative to traditional cancer treatments [153].

VT represents a paradigm shift in cancer treatment, offering precision, efficacy, and the potential for reduced side effects compared to conventional therapies. By leveraging the principles of genetic engineering, VT addresses key limitations of current treatments while opening new avenues for therapeutic innovation [154]. Table 3 highlights significant research in OVT, demonstrating its transformative potential in oncology.

Table 3. Some research progress on OVT

S/N	Year	Title	Method	Aim	Finding(s)	Advantage(s)	Disadvantage(s)	Comment(s)	Refs
1.	2020	Modelling dynamics of cancer virotherapy with immune response	ODE model Qualitative analysis Stability analysis Numerical simulation Parameter analysis	To modify the existing model, incorporate the interplay between uninfected tumour cells and the immune response into the dynamics of VT.	The qualitative analysis of the model identified five equilibrium points, one exemplifying the immune system eradicating infected cells and viruses during VT.	The original tumour undergoes a reduction in size until it reaches equilibrium.	The immune system perceives modified viruses as foreign entities, and not all viruses are eradicated post-treatment.	potential for expansion to include synergistic approaches with other therapeutic modalities and spatial progression analysis of cancer cells.	[140].
2.	2020	Modelling dynamics of cancer radio virotherapy (RVT)	Two ODEs models: VT model, RVT model. Qualitative analysis, parameter analysis, stability analysis, numerical simulation.	To model the progression of tumour proliferation in the context of RVT treatment.	RVT exhibits more efficacy than VT, presenting a viable treatment option with total tumour eradication.	RVT is a superior alternative to VT, achieving higher efficacy and total tumour eradication.	Viral entities persist within the host organism even after tumour eradication.	Extension needed to explore radiation effects on healthy tissues and integrate spatial progression of cancer cells into models.	[141].
3.	2023	Oncolytic virotherapy evolved into the fourth generation as tumour immunotherapy.	Critical review	To present an in-depth examination of the developmental trajectory and current state of OVT, focusing on processes employed to augment safety and efficacy.	OVT has evolved into the fourth generation of tumour IT, including innovative OVs expressing bispecific T cell activators (BiTAs).	Integrating OVs with immune cells shows significant potential. OVs are promising options for future therapeutic use.	Safety and efficacy remain undetermined, especially regarding specific cancers and patient outcomes.	In-depth studies on virus, cancer, and patient characteristics are needed to enhance OV effectiveness.	[148].
4.	2022	Strategies for Advanced Oncolytic Virotherapy: Current Technology Innovations and Clinical Approaches.	Comprehensive review of genetic engineering and clinical trials.	To provide insights into technological innovations and clinical applications of advanced OVT.	The review highlighted the advancements in genome engineering and delivery methods for oncolytic viruses. The safety and efficacy of genetically modified oncolytic viruses were emphasized.	Enhances immune system activation and tumor specificity while minimizing damage to normal tissues.	Challenges remain in addressing physical barriers, antiviral host immunity, and ensuring safe delivery.	Future research should focus on optimizing delivery systems and integrating OVT with other therapeutic modalities to improve efficacy.	[149].
5.	2022	Oncolytic virus-based hepatocellular carcinoma	Review on Clinical trials.	To explore the status of OVT in HCC, including delivery	Pexa-Vec, a recombinant vaccinia virus, shows high	Highlights the potential of OVT in advanced	Challenges include delivery strategies for intravenous administration and	Further research is needed to optimize OVT delivery systems	[146].

S/N	Year	Title	Method	Aim	Finding(s)	Advantage(s)	Disadvantage(s)	Comment(s)	Refs
		treatment: Current status, intravenous delivery strategies, and emerging combination therapeutic solutions.		strategies and combination therapies.	tumor selectivity and replication ability, enhancing antitumor immunity and achieving significant therapeutic effects in clinical HCC studies.	HCC with low toxicity and integration with other modalities for improved outcomes.	ensuring safety and efficacy across different patient profiles.	and explore synergies with immunotherapies and other treatments for broader applications.	
6.	2023	Oncolytic virotherapy: basic principles, recent advances, and future directions.	Review of basic principles and advances in genetic engineering of OVs.	To summarize the basic principles, classification, and recent advances in OV-modification strategies to enhance safety, efficacy, and versatility in cancer treatment.	Advanced OVs are engineered to target cancer cells with precision, promote antitumor immunity, and integrate effectively with existing therapies.	Demonstrates versatility in mechanisms, including direct oncolysis, tumor microenvironment modulation, and combination therapies.	Safety concerns remain regarding off-target effects, environmental shedding, and potential recombination of modified viruses.	Suggests continued research on targeted genetic engineering and comprehensive clinical trials to maximize the therapeutic potential of OVs while mitigating risks.	[151].
7.	2024	Enhancing cancer therapy: the integration of oncolytic virus therapy with diverse treatments	Comprehensive review	To analyze the mechanisms, advantages, potential challenges, and future directions of integrating OVT with various cancer treatments.	Highlighted the synergistic potential of OVT when combined with existing therapies, enhancing immune response and reducing tumor evasion mechanisms.	Combination therapies amplify OVT's efficacy, leveraging immune system recognition and destruction of cancer cells.	Complexities in optimizing therapy combinations and addressing adverse effects from combined modalities remain.	Future studies should focus on mechanisms enhancing integration, ensuring safety, and maximizing therapeutic benefits across diverse cancer types.	[154].
8.	2024	The Potential of Oncolytic Virotherapy in the Treatment of Head and Neck Cancer: A Comprehensive Review	Systematic review	To provide a comprehensive overview of OVT for head and neck cancer, including mechanisms, clinical studies, and future directions.	Showed promise for OVT in addressing unmet needs in head and neck cancer treatment, with advancements in targeted therapies and immune modulation.	Demonstrates the potential for integration with immunotherapies and other cancer treatments, offering a multifaceted approach to therapy.	Challenges include optimizing virus delivery, enhancing specificity, and overcoming immune resistance mechanisms in clinical applications.	Recommends prioritizing clinical trials to validate efficacy and safety, as well as advancing delivery technologies to enhance outcomes.	[143].
9.	2020	Oncolytic Virotherapy: New Weapon for Breast Cancer Treatment	Comprehensive review	To explore the role of oncolytic virotherapy in transforming the breast cancer tumor	Emphasized the potential of OVT to convert immunologically 'cold' tumors into 'hot' ones,	Provides novel insights into combining OVT with ICIs to improve treatment	The variability in patient responses and the challenges in virus delivery highlight the need	Encourages further investigation into effective delivery methods and optimizing	[153].

S/N	Year	Title	Method	Aim	Finding(s)	Advantage(s)	Disadvantage(s)	Comment(s)	Refs
				microenvironment and enhancing treatment efficacy.	increasing immune system activation and therapeutic outcomes in breast cancer.	responses in resistant breast cancer cases.	for personalized approaches.	treatment combinations to improve patient outcomes, tying these insights into a broader understanding of OVT's potential to revolutionize cancer treatment through enhanced safety, efficacy, and integration with existing therapies.	

VT: Virotherapy, OVT: Oncolytic Virotherapy, RVT: Radio Virotherapy, OV: Oncolytic Virus, and HCC: Hepatocellular Carcinoma.

Conclusions

This critical review has delved into the multifaceted landscape of cancer research and treatment, offering a comprehensive analysis of pivotal factors shaping our understanding and approach to combating this complex disease. The inherent duality of RT has been a central theme, underscoring its therapeutic potential alongside its challenges, particularly in immunomodulation and the unintended harm to normal tissues. These observations highlight the pressing need for tailored treatment strategies that balance the imperative of cancer eradication with the mitigation of collateral damage to healthy cells.

The examination of LDR effects on the brain has illuminated the necessity for rigorous studies to unravel its implications for behavioural and neurological functions. Such findings prompt a deeper reflection on the long-term cognitive and neurobiological outcomes of therapeutic interventions. Furthermore, the intricate link between cellular dysfunctions and cancer progression has been explored, illustrating how irregularities in cell division contribute to unchecked malignancy growth. This review also emphasises the innovative strides made through VT, propelled by advancements in genetic engineering, which offer precise targeting and elimination of cancer cells, presenting new avenues for effective treatment modalities.

In conclusion, this review affirms that the fight against cancer requires relentless pursuit of innovative strategies, thorough scientific inquiry, and a nuanced understanding of the interplay of various contributing factors. By advancing precision medicine and pushing the boundaries of scientific exploration, we can redefine cancer treatment paradigms and improve patient outcomes on a global scale. As researchers, clinicians, and advocates collaborate to deepen their insights into the complexities of cancer, these collective efforts inspire hope for a future where this formidable disease is met with more effective, less burdensome interventions.

Conflicts of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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