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Challenges in Radiation Therapy

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Abstract: In recent years, significant progress has been made in understanding the proposed hallmarks of cancer development and treatment. However, with its increasing prevalence, cancer clinical management remains a challenge for the twenty-first century. Radiation therapy, surgery, chemotherapy, immunotherapy, and hormonal therapy are all treatment options. Radiation therapy remains an important component of cancer treatment, with approximately half of all cancer patients receiving it during their illness and it contributes to 40% of cancer cures. The primary goal of radiation therapy is to deprive cancer cells of their ability to multiply (cell division). Cancer is one of the leading causes of mortality worldwide, and radiation therapy is used to treat more than half of all cancer patients. Radiation treatment is used to treat nearly every kind of cancer, as well as certain noncancerous tumors. It kills cancer cells with high-energy beams. X-rays are most commonly utilised in radiation treatment, however protons or other forms of energy can also be used. This indicates that radiotherapy is a promising technology. However, much like radiation, everything has its own set of advantages and disadvantages. The major benefit of radiation is that it could aid in the control of cancer development. These therapies are also frequently used to facilitate surgery for patients with diseases that are borderline resectable and those with local advanced-stage pancreatic cancer. In terms of side effects or weakness, considering on how near the region of interest is to the tumor, it may cause harm to nearby tissues such as the lungs and heart. Therefore, it will be a challenge.

Keywords: *Radiation Therapy, Radiotherapy, Cancer, Radiation*

INTRODUCTION

Radiation therapy, often known as radiotherapy, has been used to treat cancer for over a century. In terms of history, Hippocrates coined the name "cancer" from the Greek "karkinos," arguing that the origin of the disease was a humoral imbalance stored in the patient's body, a theory that remained until the nineteenth century [1]. Significant developments have occurred over the previous few years, and contemporary radiotherapy is now a well-established curative approach for cancer treatment. Radiotherapy has a strong scientific foundation, and the knowledge of cancer biology and radiobiology has vastly advanced. Oncologists and cancer specialists are the radiotherapists of today. There has been tremendous technological advancement. Local cancer treatment has been demonstrated to be the most successful, thus the future of radiation oncology looks bright [2]. With ionising radiation, mostly high-energy X-rays, radiotherapy is now a safe and extremely efficient treatment for cancer. By providing its most effective dosage possible, radiotherapy helps cancer professionals to precisely target and eradicate tumour cells [3].

PRINCIPLES OF RADIATION THERAPY

Radiation is the transfer of energy through waves or a stream of particles. It destroys a cell's genes (DNA) and some of its components. These genes carry the information for constructing functioning molecules known as proteins. Radiation destroys a cancer cell's genome, preventing it from growing and dividing. It thus indicates that cancer cells could be killed and tumors can be shrunk with radiation. Because the cell cycle phase is crucial in cancer therapy, knowing well about the usual life cycle of a cell is significant in understanding how radiation works as a treatment. Radiation usually destroys cells that are actively or rapidly dividing first. On cells that are resting or dividing slowly, it does not operate as quickly [4] [5]. Figure 1 explains the cell cycle.

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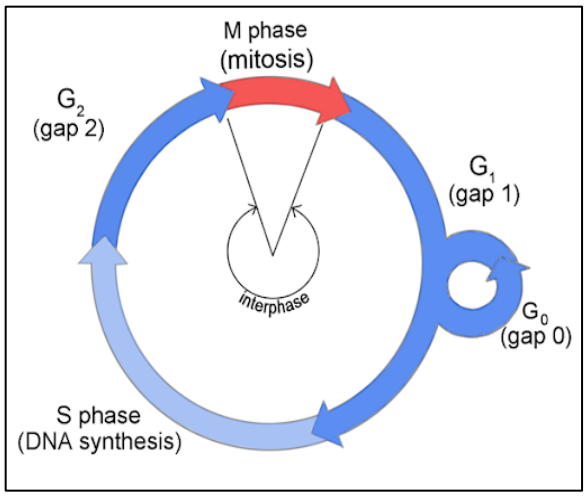

Fig 1 The cell cycle (G_0 = Cell is resting, G_1 = RNA and proteins are made, S = DNA is made, G_2 = Apparatus for mitosis is built, M = Mitosis (the cell divides into two cells) [6]

The cell cycle refers to all of the phases of cell division. A freshly formed cell enters the G_1 phase. The G_1 phase is when cells begin to differentiate. A cell can also reach a non reproductive stage termed G_0 from G_1, where it will resume its normal duties. The cell will re-enter G_1 to begin a new cell cycle when fresh cell growth is required. The cell will start producing cyclin D and cyclin E, as well as cyclin-Cdk complexes that are active. These will aid in the cell's progression to the S phase. The different active cyclin-Cdk complexes that will control the cell cycle's passage from one phase to the next are shown in the diagram's center. After the M phase, the cell divides into two new cells, completing the cycle [7].

TYPES OF RADIATION THERAPY

External radiation, internal radiation, and systemic radiation are the three forms of radiation treatment. The type of radiation utilized is determined by the type of cancer and its location in the patient's body. In other circumstances, though, more than one kind is employed. This can destroy cells or modify their DNA, preventing them from growing.

a) External Radiation: The most prevalent form of radiation used in cancer therapy is external beam radiation. This form of radiation employs an external equipment that is located outside of the body to deliver radiation towards the cancerous spot. External beam radiation treatment is well suited to treating wide regions or several portions of the body at the same time. Although it is intended to target malignant cells, it frequently damages healthy tissue as well [8]. Figure 2 shows how external beam radiation therapy looks like.

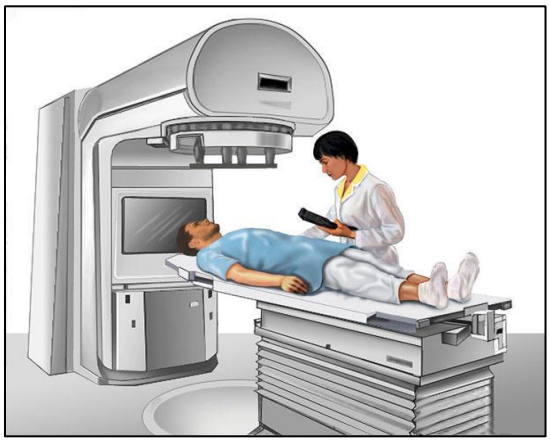

Fig 2 External Beam Radiation Therapy [9]

b) Internal Radiation: Internal radiation, sometimes known as brachytherapy, involves the placement of a radioactive source inside the body, either near or in the tumor. A radiation source is generally contained in a tiny structure called an implant in this form of treatment. To harm as few normal cells as possible, the implant is put very close to or inside the tumor. Internal radiation therapy enables for a larger dosage of radiation to be delivered in a smaller area than external radiation therapy [10].

c) Systemic Radiation: Some kinds of cancer are treated using systemic radiation, which involves the use of radioactive drugs. These drugs could be taken by mouth or injected into a vein using a needle. They move through into the body, locate the cancer, and emit radiation [11].

THE PROS AND CONS OF RADIOTHERAPY

Radiation therapy has become an exciting initiative and treatment to cancer patients especially. Despite being aware of the side effects that can be found during or after undergoing treatment, but with the knowledge and research possessed by experts today, they will do their best to provide treatment without causing incurable effects. Here are some of the pros and cons of radiotherapy;

The Pros of Radiotherapy

a) Treat or shrink cancer in its early stages

Some tumors are extremely radiation-sensitive. In many circumstances, radiation may be used alone to reduce or eliminate the tumour altogether. A few rounds of chemotherapy are sometimes administered first. For some malignancies, radiation treatment could be used before surgery as pre-operative or neoadjuvant therapy

to decrease the tumor, either after surgery as adjuvant treatment to help avoid the cancer from returning [12]. Some chemotherapy medications or drugs operate as radiosensitizers, causing cancer cells to become more susceptible to radiation. As a result, radiation can be used with chemotherapy (chemo), and these treatments improve the effectiveness of the radiation.

b) Treatment for cancer recurrences (coming back)

It's referred to as a recurrence when cancer reappears after a time of remission. Some cancer cells could persist even after therapy. These cells have the ability to spread, which might result in symptoms. These cells might be in the same spot where the cancer started or in a different section of the body. Thus, getting adequate radiation treatment on a regular basis as recommended by experts can reduce the chances for the cancer to spread again [13].

The Cons of Radiotherapy

Caused cardiotoxicity

Cardiotoxicity is a term used to describe how radiation therapy used in cancer treatment might create complications with the heart and vascular (circulation) system. It can occur days or months after exposure, although it is more common years afterwards. Cardiotoxicity can lower a patient's quality of life and raise the chance of death from cardiovascular disease. When a big volume of heart muscle is subjected to a high dosage of radiation, cardiotoxicity is a concern [14].

Depression and fatigue

Fatigue is a common and frustrating symptom among cancer patients. It exacerbates suffering and can be found in all kinds and stages of the disease. This one has been discovered to be an issue prior to, during, and after therapy, and to persist long after treatment has ceased, even in persons who are thought to be disease-free [15]. Fatigue, rather than the pain, nausea, and vomiting associated with illness and therapies, is frequently cited as the most unpleasant side effect of radiation therapy by cancer patients [16].

Radiation is a physical agent used to kill cancer cells. Ionizing radiation is used because it produces ions (electrically charged particles) and deposits energy in the cells of the tissues it passes through. This deposited energy has the potential to kill cancer cells or cause genetic changes that result in cancer cell death [17]. High- energy radiation damages cells' genetic material (deoxyribonucleic acid, DNA), preventing them from dividing and proliferating further. Although radiation causes damage to both normal and cancer cells, the goal of radiation therapy is to maximise radiation dose to abnormal cancer cells while minimising exposure to normal cells adjacent to cancer cells or in the path of radiation. Normal cells can usually repair themselves faster and maintain their normal function status than cancer cells. Cancer cells in general are less efficient than normal cells at repairing radiation-induced damage, resulting in differential cancer cell killing [18].

Radiation can be used as a curative treatment as well as a very effective palliative treatment to relieve cancer- related symptoms in patients. Radiation therapy may also be used in conjunction with other treatment modalities such as surgery, chemotherapy, or immunotherapy. Radiation, when used prior to surgery (neoadjuvant therapy), aims to shrink the tumour. Radiation, when used after surgery (adjuvant therapy), destroys microscopic tumour cells that may have been left behind. Tumours differ in their sensitivity to radiation treatment, as is well known.

Table 1. Common cancers that are treated with radiation therapy.

Early cancers curable with radiation therapy alone	Cancers curable with radiation therapy in combination with other modalities
Skin cancers (squamous and based cell)	Breast carcinomas
Prostate carcinomas	Rectal and anal carcinomas
Lung carcinomas (non-small cell)	Local advanced cervix carcinomas
Cervix carcinomas	Locally advanced head and neck carcinomas
Lymphomas (Hodgkin's and low-grade non-Hodgkin's)	Locally advanced lung carcinomas
Head and neck carcinomas	Advanced lymphomas Bladder carcinomas Endometrial carcinomas CNS tumours Soft tissue sarcomas Pediatric tumours

There are two methods for delivering radiation to the cancer's site. External beam radiation is supplied from the outside of the body by directing high-energy rays (photons, protons, or particle radiation) to the tumour's site. In the clinical setting, this is the most common strategy. Internal radiation, also known as brachytherapy, is given to the tumour site from within the body using radioactive sources sealed in catheters or seeds. Because of its short- term effects, it is commonly used in the routine treatment of gynaecological and prostate cancers, as well as in circumstances where retreatment is required [17].

SIDE EFFECTS OF RADIATION THERAPY

Acute radiation damage mostly affects quickly growing cells, such as epithelial skin surfaces and the gastrointestinal system. Radiation affects stem cells, resulting in tissue loss as a result of regular cell turnover but insufficient stem cell replenishment due to radiation damage [19]. This causes a rupture in the protective barrier, which occurs most commonly in the skin, oral mucosa, and gastrointestinal system, especially 1-5 years after radiotherapy is completed. As a result of compensatory hyperplasia inside stem cells, recovery occurs. As a result, symptoms subside within a few weeks. Such lesions are consequential late effects when acute injury does not heal completely and lingers into the late phase. Such consequences are more common in chemotherapy-radiotherapy regimens, where tissues fail to heal due to concurrent cytotoxic effects from chemotherapy.

Late problems arise in slow-turning tissues such as the brain, kidney, liver, intestinal wall, subcutaneous tissue, adipose tissue, and muscle. Radiation causes fibrosis, atrophy, necrosis, and vascular damage resulting in telangiectasia and carcinogenesis in these tissues. A complicated interplay of different cytokines and adaptive cellular mechanisms causes late effects. Damage to the vasculature causes increased permeability, which promotes collagen deposition by releasing vasoactive cytokines, TGF-beta, and fibrin. The majority of these tissues or organs have a dosage threshold at which late effects become more pronounced [20]. The production of thrombi and subsequent distal ischemia caused by leucocyte adherence to injured endothelial cells culminates in distal atrophy and necrosis. The cytokine storm and dysregulated cellular connections may be perpetuated if more cells are lost. The various responses of tissues to irradiation are due to the diverse types of cytokines released, which are dependent on tissue type. For example, fibrosis is the most common response in the lungs, while necrosis is the most common response in the brain [21].

Radiation injury is caused by a complex interaction of radiobiologic variables, intrinsic radiosensitivity, the volume of irradiated tissue or organ, total dose, dosage per fraction, the severity of immediate effects, and surgery and chemotherapy [22]. The phrases minimal tolerance dose (TD 5/5) and maximum tolerated dose (TD 50/5) refer to the doses at which serious life-threatening problems occur in 5% and 50% of patients after five years of radiation, respectively [23]. According to experimental evidence, fraction size is the most important determinant in determining late effects [24]. Old age, BMI, anaemia, associated infection, comorbid diseases, concomitant chemotherapy regimens, and inherent radiosensitivity of organs at risk are host-related variables that impact the probability of late sequelae.

The sensitivity and responsiveness of all tissues to radiation damage varies. Irritation sites that are commonly encountered, as well as the difficulties that come with them, are discussed. Skin and Mucosa is an acute response in the head and neck that includes erythema, inflammation, and desquamation of dry and wet surfaces, resulting in mucositis, pruritis, hypersensitivity, discomfort, and ulcers in the mucosa [25]. If mucositis is severe, it might make it difficult to eat and need the use of a feeding tube. These acute reactions normally heal at the conclusion of treatment or can lead to long-term consequences. Alopecia, telangiectasia, fibrosis of the masticator muscles resulting in trismus, changes in taste sensations, and dysphagia are examples of subsequent consequences. In 5- 10% of patients with skin and muscular fibrosis, trismus develops. Severe mucositis linked with head and neck tumours causes eating difficulties, which are exacerbated by cancer cachexia, and hampers healing and stress response. Oral hygiene, topical analgesics, dietary modification, opioid analgesics, doxepin rinses, antacid diphenhydramine mouthwash, mucoadhesive hydrogel, and enteral tube feeding are all used to treat severe mucositis.

Salivary Glands, Salivary gland irradiation can cause apoptosis, which can cause swelling and soreness after the first dosage of treatment, escalating to xerostomia and severe dental cavities and osteonecrosis, as well as problems wearing dentures, eating, and speaking. If salivary gland function is restored, it can take months or years [26]. Appropriate oral hygiene and dental care, including fluoride therapy, chlorhexidine rinses, and regular follow-up with a dentist, are all part of the treatment for xerostomia problems. Fatigue, lack of appetite, nausea, vomiting, headaches, hearing loss, acute encephalopathy (rare), and worsening neurologic symptoms are some of the initial consequences of cranial irradiation on the nervous system (due to edema of the irradiated tumour and surrounding tissues). Persistent weariness, neurocognitive consequences, cerebrovascular disease, neuroendocrine dysfunction, and secondary cancers are examples of long-term neurologic sequelae [27].

Irradiation of the spinal cord can cause acute transitory myelopathy due to demyelination, which manifests as Lhermitte syndrome. Lower motor neuron syndrome, telangiectasias, and consequent bleeding are examples of late consequences [28]. Progressive myelopathy causes a wide range of permanent neurologic deficits, from minimal sensory complaints to total paralysis. To treat radiation myelopathy, experimental research and anecdotal data indicate the use of glucocorticoids, hyperbaric oxygen, or bevacizumab, which may result in partial recovery [29].

Irradiation is commonly used to treat malignancies of the thorax, breast, lung, oesophageal, and lymphatic systems. Congestion, cough, dyspnea, fever, and chest pain produced by radiation pneumonitis are some of the early clinical symptoms of lung irradiation. Infiltrates within the irradiation region are revealed by radiographic examinations. Hypoxia and eventual right-sided heart failure occur in severe situations. Partially irradiating the lungs can cause bilateral immune-mediated pneumonitis, which usually goes away on its own [30]. The natural course of pneumonitis is either a slow resolution of the acute phase followed by a chronic phase of inflammation and fibrosis that takes months to years to develop. Because the degree of fibrosis is related to the area irradiated, the patient may develop restrictive lung disease with cough, shortness of breath, chest discomfort, and a significant loss in diffusion capacity and breathing volume if a large area is irradiated [31]. A PET scan distinguishes a tumour from a radiation injury because the appearance is comparable to tumour recurrence. Early radiation pneumonitis is treated with a thorough evaluation to rule out alternative causes of acute respiratory distress, as well as the use of systemic steroids with a progressive taper.

Acute pericarditis, pericardial effusion, constrictive pericarditis, valve dysfunction, conductive system malfunction, and myocardial fibrosis are all symptoms of radiation injury to the heart [32]. Ischemic heart disease is increased by radiation therapy because it causes myocardial microvascular disease or macrovascular coronary artery stenosis [33]. The great majority of acute morbidity is linked to the use of chemotherapy and hormone therapy at the same time; as a result, personalised treatment strategies can help reduce the risk of immediate cardiac effects. Prior to radiation therapy (RT), myocardial nuclear imaging investigations can help with risk classification and irradiation dose and method. Radiation cardiotoxicity has long-term consequences that manifest ten years after RT and contribute to a high mortality rate in younger women diagnosed with breast cancer [34].

DRUGS IN DEVELOPMENT

One of the most difficult aspects of radiotherapy is that some tissues are extremely susceptible to radiation but are present right next to the tumour. Prostate cancer, for example, has a reasonably high cure rate with radiotherapy, but the patient suffers considerable side effects as a result of treatment since high dosages and conjunction with hormone therapy are required. Drugs that can sensitise only tumours to radiation are needed to avoid normal tissue damage. These medications have the potential to increase response rates while reducing undesired side effects.

Inhibitors of double-stranded break repair and inhibitors of the DNA damage response are among the medications being developed as radiation therapy sensitizers. Because radiation causes DNA single-stranded and double- stranded breaks, adding an attack on the mechanisms that repair these forms of damage is thought to result in a one-two punch that kills tumour cells. Normal cells, on the other hand, will be able to repair their genomes if their damage response pathways are intact and there are no genetic alterations that hinder repair. The MRN complex, which is involved in DNA double-stranded break repair, as well as components of the homologous and nonhomologous recombination processes, are now being studied.

Inhibitors of poly (ADP-ribose) polymerase (PARP) are now being tested in clinical studies for various solid tumours in conjunction with chemotherapy and radiotherapy. PARP is a protein that helps cells repair DNA damage. Inhibitors of the histone deacetylase (HDAC) enzyme are also in the early phases of development. HDACs help to make higher-order DNA structures more compact. According to published studies, inhibiting these enzymes may obstruct the cell's ability to efficiently repair DNA. Another method is to use inducers of cell- cycle arrest to make cells more sensitive to radiation therapy-induced DNA damage, which could lead to more efficient tumour cell killing. Several drugs that elicit cell-cycle arrest are now being tested in clinical trials. Anti- angiogenesis treatments, immunological modulators, and inhibitors of apoptosis, or programmed cell death, are just a few of the targeted

therapeutics being developed to improve radiotherapy [35].

IDENTIFYING RADIATION TOXICITY GENES IN NORMAL TISSUES

Acute radiotoxicity and late consequences such as telangiectasia, edoema, and fibrosis are examples of radiation toxicity in normal tissues. Radiation-induced fibrosis, a late occurrence that normally occurs 4 months to many years following radiation, is of particular concern. Fibrosis can develop in a variety of organs, depending on the dose, volume of irradiated tissue, and tissue types exposed to irradiation. As cancer patients' survival times have increased, their quality of life has deteriorated dramatically, and in certain cases, death has resulted [36]. Radiation-induced fibrosis is thought to follow a similar mechanism to chronic wound healing processes [37]. Radiation-induced fibrosis is thought to be caused by complex molecular signalling involving cytokines, growth factors, integrins and cell adhesion, stress response and DDR, and extracellular matrix remodelling, which results in the formation of myofibroblasts, which have a different cell architecture.

Using patient-derived fibroblasts in culturing [38] or peripheral lymphocytes [39], several investigations have documented variations in gene expression profiles between samples generated from patients with and without radiation-induced fibrosis. However, no confirming "gene expression signatures" for predicting radiation-induced fibroblasts have emerged from this research. 87 differentially expressed genes were identified in a gene expression profiling of whole blood from breast cancer survivors with and without fibrosis 3-7 years after radiation therapy, including genes downregulated during the maintenance phase of fibrosis as opposed to genes upregulated during the early, initiating phase of fibrosis. Upregulation of genes implicated in TGF-1 signalling was common [40].

Several preclinical techniques have been developed to target radiation-induced fibrosis in mice at diverse organ locations, either by inhibiting matrix production or decreasing inflammation [41]. TGF-1 receptor inhibitor LY2109761 was reported to reduce radiation-induced inflammation and pulmonary fibrosis, as well as prolong survival, in one lung cancer model [42]. These findings prompted a phase I/II study in SCLC patients employing stereotactic ablative irradiation in combination with an anti-TGF-1 antibody (fresolimumab) to see if fresolimumab can reduce radiation-induced cytotoxicity. There was no difference in overall survival or disease- free survival in a randomised clinical trial in which pentoxifylline and vitamin E were given for 6 months following breast wall irradiation, but fibrosis was dramatically reduced in the treated group [43].

TECHNOLOGICAL ADVANCES

The purpose of radiotherapy is to give the tumour as much radiation as possible while sparing healthy tissue. New imaging modalities, more powerful computers and software, and new delivery systems like as sophisticated linear accelerators have all contributed to this success.

2D radiation therapy employing rectangular fields based on plain X-ray imaging has been substantially supplanted by 3D radiation therapy using CT imaging, which provides exact localization of the tumour and key normal organ structures for optimal beam placement and shielding. The goal is to deliver radiation to the gross tumour volume (GTV), with a clinical target volume (CTV) for microscopic tumour expansion and a planning target volume (PTV) for additional margin uncertainty due to organ mobility and setup variables [44].

The oncologist can use intensity modulated radiation therapy (IMRT) to provide irregular-shaped radiation doses that adhere to the tumour while avoiding important organs. Inverse planning software and computer-controlled intensity-modulation of numerous radiation beams during treatment make IMRT possible. IMRT can now be administered by linear accelerators with static or dynamic multi-leaf collimators or tomotherapy equipment in several clinical departments. This has resulted in therapeutic ratio improvements for a variety of tumour types, including head and neck cancers, prostate cancers, and gynaecological cancers [45].

As treatment margins become tighter and more conformal in image-guided radiotherapy (IGRT), the risk of missing tumour due to organ motion and patient setup differences increases [46]. When essential tissues are adjacent to the tumour, even a minor positioning error can result in accidental radiation of normal organs. IGRT enables for the detection and repair of such faults using information obtained from pre-radiotherapy imaging. One

example is the use of daily cone-beam CT scans prior to each treatment [47]. Because of the increased accuracy, dosage escalation is now possible [48], which has improved the therapeutic ratio for a variety of tumour types, including head and neck cancers [49] and prostate cancers [50].

SBRT (Stereotactic body radiation therapy), which precisely delivers very high individual doses of radiation over only a few treatment fractions to ablate tiny, well-defined primary and oligometastatic tumours anywhere in the body [51], is made possible by the foregoing technological breakthroughs. Any tissue immediately close to the tumour is likely to be destroyed due to the high radiation exposure. Clinically relevant toxicity is rare since the quantity of normal tissue in the high dosage zone is tiny and non-eloquent [52]. SBRT has proved to be effective in treating early-stage non-small cell lung cancer in patients who are unable to undergo surgery. Prostate, head and neck, hepatic, renal, oligometastases, spinal, and pancreatic tumours are among the others [53].

CONCLUSION

With continued attempts to build new radiation treatment modalities and procedures that continue to improve the survival and quality of life of cancer patients, radiation remains an important modality for cancer treatment. Radiation therapy-related toxicities have become a focus as clinical results of cancer treatment have improved. Through dose fractionation and conformal radiation treatments, the sparing of normal cells/tissues has increased thanks to the introduction of mechanistic biological studies and advancements in radiation technology. Radiation is also being used in conjunction with molecular targeted therapy in order to improve the radiation treatment's therapeutic ratio. Because of its capacity to destroy cancer cells and stop tumors from developing, radiation therapy is among the most popular treatments. It can be used alone or in conjunction with other types of therapy. Patients getting treatment should be educated about all of the potential negative effects of radiation. By doing specific tests and imaging before starting radiation therapy, the treating specialist will evaluate an individual patient's risk for any impact or disease. If a patient is in risk, the radiation oncologist may reduce the quantity of radiation provided during treatment or do something alternative. This is because the objective is to strike a balance between the advantages of cancer treatment and the risk of cardiac damage and many more.

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REFERENCES

[1] Paulo Martins. 2018. A brief history about radiotherapy. International Journal of Latest Research in Engineering and Technology 4 (2), 8-11.

[2] Holsti, L. R. 1995. Development Of Clinical Radiotherapy Since 1896. Acta Oncol. 34(8), 995-1003.

[3] Joanna Kazmierska, Núria Jornet Sala, Michelle Leech, Barbara Alicja Jereczek-Foss, Yolande Lievens and John Yarnold. 2018. Radiotherapy: Seizing the opportunity in cancer care. Marie Curie Legacy 1-16.

[4] Radiation Therapy Principles. 2011. American Cancer Society 1-21.

[5] National Institutes of Health. 2021. Help Me Understand Genetics: How Genes Work. Reprinted from MedlinePlus Genetics. 1-20.

[6] Harvard College. 2007. Cell Cycle. Harvard. Edu. Life Sciences Cyberbridge.

[7] Richard J. Reynolds and Jay A. Schecker. 1995. Radiation, Cell Cycle, and Cancer 23, 1-39.

[8] Yolanda Smith. 2021. Radiation Therapy Types. News-Medical Life Sciences.

[9] National Cancer Institute. 2018. External Beam Radiation Therapy for Cancer.

[10] A Guide to Radiation Therapy. 2016. American Cancer Society 1-47.

[11] Radiation Therapy; What It Is, How It Helps. 2020. American Cancer Society 1-16.

[12] The Science Behind Radiation Therapy. 2014. American Cancer Society 1-21.

[13] When cancer returns: How to cope with cancer recurrence. Mayo Clinic(2021)

[14] Radiation Heart Disease: Radiation Therapy and the Heart. 2021. Cleveland Clinic.

[15] Brown LF and Kroenke K. 2009. Cancer-related fatigue and its associations with depression and anxiety: a systematic review. Psychosomatics 50(5), 440- 447.

[16] National Comprehensive Cancer Network. 2009. Clinical practice guidelines in oncology. Cancer-related fatigue.

[17] Baskar, R., Lee, K. A., Yeo, R., and Yeoh, K. W. 2012. Cancer and radiation therapy: current advances and future directions. International journal of medical sciences 9(3), 193–199.

[18] Begg, A. C., Stewart, F. A., and Vens, C. 2011. Strategies to improve radiotherapy with targeted drugs. Nature Reviews Cancer 11(4), 239-253.

[19] Dewey WC, Furman SC and Miller HH. Comparison of lethality and chromosomal damage induced by x- rays in synchronized Chinese hamster cells in vitro. 1970. Radiat Res. 43(3), 561-81.

[20] Rubin P, Johnston CJ, Williams JP, McDonald S and Finkelstein JN. 1995. A perpetual cascade of cytokines postirradiation leads to pulmonary fibrosis. Int J Radiat Oncol Biol Phys. 33 (1), 99-109.

[21] Coderre JA, Morris GM, Micca PL, Hopewell JW, Verhagen I, Kleiboer BJ and Van der Kogel AJ. 2006. Late effects of radiation on the central nervous system: role of vascular endothelial damage and glial stem cell survival. Radiat Res. 166 (3), 495-503.

[22] Stone HB, Coleman CN, Anscher MS and McBride WH. 2003. Effects of radiation on normal tissue: consequences and mechanisms. Lancet Oncol. 4 (9), 529-36.

[23] Mohanti BK and Bansal M. 2005. Late sequelae of radiotherapy in adults. Support Care Cancer. 13(10), 775-80.

[24] Hall EJ. 2006. Intensity-modulated radiation therapy, protons, and the risk of second cancers. Int J Radiat Oncol Biol Phys. 65(1), 1-7.

[25] Dörr W, Hamilton CS, Boyd T, Reed B and Denham JW. 2002. Radiation-induced changes in cellularity and proliferation in human oral mucosa. Int J Radiat Oncol Biol Phys. 52(4), 911-7.

[26] Cooper JS, Fu K, Marks J and Silverman S. 1995. Late effects of radiation therapy in the head and neck region. Int J Radiat Oncol Biol Phys. 31(5), 1141-64.

[27] Mehta P, Fahlbusch FB, Rades D, Schmid SM, Gebauer J and Janssen S. 2019. Are hypothalamic- pituitary (HP) axis deficiencies after whole brain radiotherapy (WBRT) of relevance for adult cancer patients? - a systematic review of the literature. BMC Cancer 19(1), 1213.

[28] Mikami T, Kato I, Nozaki F, Umeda K, Kamitori T, Tasaka K, Ogata H, Hiramatsu H, Arakawa Y and Adachi S. 2018. Sudden spinal hemorrhage in a pediatric case with total body irradiation-induced cavernous hemangioma. Pediatr Blood Cancer. 65(10), e27250.

[29] Wong CS, Fehlings MG and Sahgal A. 2015. Pathobiology of radiation myelopathy and strategies to mitigate injury. Spinal Cord. 53(8), 574-80.

[30] Morgan GW and Breit SN. 1995. Radiation and the lung: a reevaluation of the mechanisms mediating pulmonary injury. Int J Radiat Oncol Biol Phys. 31(2), 361-369.

[31] McDonald S, Rubin P, Phillips TL and Marks LB. 1995. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. Int J Radiat Oncol Biol Phys. 31(5),1187-203.

[32] Adams MJ, Hardenbergh PH, Constine LS and Lipshultz SE. 2003. Radiation-associated cardiovascular disease. Crit Rev Oncol Hematol. 45(1), 55-75.

[33] Taylor C, McGale P, Brønnum D, Correa C, Cutter D, Duane FK, Gigante B, Jensen MB, Lorenzen E, Rahimi K, Wang Z, Darby SC, Hall P and Ewertz M. 2018. Cardiac Structure Injury After Radiotherapy for Breast Cancer: Cross-Sectional Study With Individual Patient Data. J Clin. Oncol. 36(22), 2288-2296.

[34] Darby S, McGale P, Peto R, Granath F, Hall P and Ekbom A. 2003. Mortality from cardiovascular disease more than 10 years after radiotherapy for breast cancer: nationwide cohort study of 90 000 Swedish women. BMJ. 326 (7383), 256-7.

[35] Azvolinsky, A. 2020. Latest Advances and Challenges in Radiation Oncology. Cancer Network.

[36] Weigel C, Schmezer P, Plass C and Popanda O. 2015. Epigenetics in radiation-induced fibrosis. Oncogene. 34, 2145–2155.

[37] Yarnold J and Brotons MC. 2010. Pathogenetic mechanisms in radiation fibrosis. Radiother and Oncol. 97,149–161.

[38] Forrester HB, Li J, Leong T, McKay MJ and Sprung CN. 2014. Identification of a radiation sensitivity gene expression profile in primary fibroblasts derived from patients who developed radiotherapy-induced fibrosis. Radiothera Oncol. 111, 186–193.

[39] Svensson JP, Stalpers LJ, Esveldt-van Lange RE, Franken NA, Haveman J, Klein B, Turesson I, Vrieling H and Giphart-Gassler M. 2006. Analysis of gene expression using gene sets discriminates cancer patients with and without late radiation toxicity. PLoS medicine. 3, e422.

[40] Landmark-Hoyvik H, Dumeaux V, Reinertsen

KV, Edvardsen H, Fossa SD and Borresen-Dale AL. 2011. Blood gene expression profiling of breast cancer survivors experiencing fibrosis. Internat J Radiat Oncol, Biol, Physics. 79, 875–883.

[41] Straub JM, New J, Hamilton CD, Lominska C, Shnayder Y and Thomas SM. 2015. Radiation-induced fibrosis: mechanisms and implications for therapy. J Cancer Res and Clin Oncol. 141, 1985–1994.

[42] Flechsig P, Dadrich M, Bickelhaupt S, Jenne J, Hauser K, Timke C, Peschke P, Hahn EW, Grone HJ, Yingling J, Lahn M, Wirkner U and Huber PE. 2012. LY2109761 attenuates radiation-induced pulmonary murine fibrosis via reversal of TGF-beta and BMP-associated proinflammatory and proangiogenic signals. Clin Cancer Res. 18, 3616–3627.

[43] Jacobson G, Bhatia S, Smith BJ, Button AM, Bodeker K and Buatti J. 2013. Randomized trial of pentoxifylline and vitamin E vs standard follow-up after breast irradiation to prevent breast fibrosis, evaluated by tissue compliance meter. Internat J Radiat Oncol, Biol, Phys. 85, 604–608.

[44] International Commission on Radiation Units. Prescribing, recording and reporting photon beam therapy. Supplement to ICRU Report 50. Bethesda: International Commission on Radiation Units and Measurement. MD: ICRU; 1999.

[45] Mundt AJ, Lujan AE, Rotmensch J, Waggoner SE, Yamada SD, Fleming G and Roeske JC. 2002. Intensity- modulated whole pelvic radiotherapy in women with gynecologic malignancies. Int J Radiat Oncol Phys. 52,1330–1337.

[46] Langen KM and Jones DT. 2001. Organ motion and its management. Int J Radiat Oncol Biol Phys. 50, 265– 278.

[47] Jaffray DA, Siewerdsen JH, Wong JW and Martinez AA. 2002. Flat-panel cone-beam computed tomography for image-guided radiation therapy. Int J Radiat Oncol Biol Phys. 53, 1337–1349.

[48] Gill S, Thomas J, Fox C, Kron T, Rolfo A, Leahy M, Chander S, Williams S, Tai KH, Duchesne GM and Foroudi F. 2011. Acute toxicity in prostate cancer patients treated with and without image-guided radiotherapy. Radiat Oncol. 6, 145.

[49] Duma MN, Kampfer S, Wilkens JJ, Schuster T, Molls M and Geinitz H. 2010. Comparative analysis of an image-guided versus a non-image-guided setup approach in terms of delivered dose to the parotid glands in head-and-neck cancer IMRT. Int J Radiat Oncol Biol Phys. 77, 1266–1273.

[50] Barney BM, Lee RJ, Handrahan D, Welsh KT, Cook JT and Sause WT. 2011. Image-guided radiotherapy (IGRT) for prostate cancer comparing kV imaging of fiducial markers with cone beam computed tomography (CBCT) Int J Radiat Oncol Biol Phys. 80, 301–305.

[51] Lo SS, Fakiris AJ, Chang EL, Mayr NA, Wang JZ, Papiez L, Teh BS, McGarry RC, Cardenes HR and Timmerman RD. 2010. Stereotactic body radiation therapy: a novel treatment modality. Nat Rev Clin Oncol. 7, 44–54.

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

[53] Wu QJ, Wang Z, and Yin FF. 2008. The impact of respiratory motion and treatment technique on stereotactic body radiation therapy for liver cancer. Med Phys. 35, 1440–1451.