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Review Article

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Recent advances in radiotherapy and its side effects in the treatment of cancer

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Abstract According to Thun, DeLancey, Centre, Jemal, and Ward (2009), cancer ranks as the third most significant contributor to both morbidity and mortality on a global scale. Despite the absence of dedicated pharmaceutical interventions, radiotherapy (RT) serves as the primary therapeutic modality for cancer, with more than 60% of cancer instances necessitating radiation therapy. Radiation therapy, often known as irradiation or X-ray therapy, is a commonly used term to describe a medical treatment technique. The process of radiation induces damage to the DNA of cancer cells, leading to the disruption of their growth and division, ultimately resulting in their demise. Radiation can also impact adjacent normal cells in close proximity to cancerous cells. Despite the widespread global usage of RT, it is associated with numerous adverse effects. The relationship between radiation exposure and the incidence of cancer has been investigated through epidemiological studies conducted on survivors of atomic bomb explosions. Radiation treatment is employed as a therapeutic modality for the management of malignancies in their first stages. One significant constraint associated with radiotherapy is the adverse impact it has on the healthy cells in the vicinity of the cancerous tumour. Approximately 5% of cancer patients who are sensitive to radiation are subjected to restricted doses of radiation in order to mitigate the occurrence of severe side effects associated with radiotherapy. In the field of radiation biology, it is necessary to first identify predictors that are associated with an elevated level of radiosensitivity prior to initiating any form of treatment. This procedure facilitates the identification of patient-specific radiotherapy. The administration of radiation doses to patients varies depending on the specific types of cancers being treated. The dosage of radiation administered to the patient may vary based on factors such as the size of the tumour, the type of surgery performed, the involvement of lymph nodes, and the characteristics of the malignancy. This article provides an overview of current advancements in radiation therapy treatments for different types of malignancies and the corresponding adverse effects. Investigating the physiological and genetic concerns linked with radiation therapy is currently a pressing requirement. Therefore, the purpose of this brief review was to gather data regarding the potential hazards associated with radiotherapy and to determine whether ayurvedic medicines can mitigate their detrimental effects.

Keywords Radiotherapy, Advancements in Radiotherapy, Side-Effects of Radiotherapy

1. Radiotherapy

Radiotherapy is primarily employed as a therapeutic modality for cancer, however certain non-malignant conditions, such as arterio-venous malformations in the central nervous system (CNS) and thyroid eye disease, can also be managed with the application of radiation therapy Citrin, D. E., (2017). A significant number of cancer patients get radiotherapy, which is administered with the intention of achieving curative or palliative outcomes. Radiotherapy may be employed as a standalone treatment or in conjunction with other therapeutic modalities for cancer.

On a global scale, external beam radiotherapy is widely utilized as the predominant kind of radiotherapy, with the bulk of therapeutic interventions being administered through the utilization of a linear accelerator. In contrast, brachytherapy involves the insertion of a radioactive source into the body in order to administer a dose to a specific and precisely defined anatomical region. The dose distribution of brachytherapy is typically more advantageous compared to external beam radiotherapy, resulting in a greater preservation of normal tissues from radiation exposure. Nevertheless, brachytherapy necessitates an intrusive medical intervention and is commonly employed in the management of cervical and prostate cancer.

Contemporary external beam radiation predominantly employs high-energy photons, while the utilization of electrons is less common. Photons, being electrically neutral and devoid of mass, exhibit a greater ability to traverse the epidermis and enter deeper into the body compared to electrons, which are better ideal for treating superficial cancers. Charged particles, such as protons and carbon ions, have a limited capacity to deposit energy in surface tissues, while electrons, although also charged particles, are typically not included in this classification. Furthermore, it is worth noting that charged particles exhibit a phenomenon known as the Bragg peak, wherein they release their energy in a concentrated manner near the termination point of their trajectory. Beyond the Bragg peak, there is no emission of radiation.

Charged particles have the ability to mitigate the "low-dose bath" phenomenon associated with photon-based therapy, making them advantageous in specific anatomical sites, such as skull-base cancers.

The precision of delivering radiation beams to target tumour tissue can reach sub-millimetre levels using contemporary linear accelerators. Nevertheless, it is important to note that radiation can also have adverse effects on normal tissue, resulting in toxic consequences. Radiotherapy is typically administered to a localised region of the body in a significant proportion of patients. Additionally, the administration of radiation occurs in incremental doses, known as fractions, with the intention of selectively eliminating a greater number of cancerous cells in comparison to healthy cells. Total body irradiation (TBI) can be considered a systemic therapeutic approach; nonetheless, it is administered selectively for a limited number of specific purposes, such as its inclusion in the conditioning regimen prior to bone marrow transplantation.

Radiotherapy has been found to potentially result in short-term toxicity and long-term repercussions. Short-term unfavourable effects manifest either during the course of therapy or within a period of three months following radiotherapy, whereas late effects become apparent subsequently. The resolution of short-term or acute toxicity, such as mucositis, often occurs within a timeframe ranging from several weeks to a few months. Late consequences, such as fibrosis, are commonly seen as irreversible and exhibit a progressive nature as time passes. The extent and timing of radiation toxicity are significantly influenced by the specific tissue being treated. These consequences encompass a range of outcomes, such as acute gastrointestinal (GI) damage, cardiac toxicity, cognitive impairment, reproductive abnormalities, deformity and impairments to bone formation, hair loss, and the development of secondary malignancies.

While the implementation of multimodal therapy for cancer has led to improved patient survival rates, there is a growing concern regarding the potential for late treatment-related damage in a larger population. There has been a notable rise in the population of old and vulnerable individuals who are able to endure or coexist with their cancer diagnosis. It is common for patients to present with several comorbidities and engage in polymedication, both of which have the potential to impact the efficacy of radiation. It is important to note that symptoms experienced during and during radiotherapy may not necessarily be attributed to radiation exposure. The underlying causes of specific symptoms, such as dyspnea, can vary significantly and require distinct treatment approaches. This underscores the significance of conducting a comprehensive differential diagnosis. Furthermore, it is noteworthy to acknowledge the prolonged impact of radiation toxicity on those who have survived childhood cancer.

This Primer provides a comprehensive introduction of radiation toxicity, emphasising practical consequences of mechanisms rather than delving into technical and traditional radiobiological ideas. The toxicity associated with systemic intravenous radioisotope treatment is not a topic of discussion, despite the fact that the general principles of radiation toxicity are applicable in these circumstances.

2. Radiotherapy as a treatment for cancer

X-rays were discovered by Wilhelm Röntgen in 1895, and during the same year, the first instance of palliative treatment with X-ray beams was administered to a patient with cancer. In the subsequent progression, Claudius Regaud conducted an experiment in 1906 wherein he established that the administration of a solitary dose of X-ray radiation induced significant harm to the skin and subcutaneous tissues of rabbits. Conversely, when the same dose was administered in smaller increments (known as fractions), no harm was inflicted upon the healthy tissues. However, the animals were still rendered sterile, suggesting that the radiation specifically targeted rapidly proliferating cells,

such as gametes. The aforementioned finding validated the utilization of fractionation and highlighted the contrasting impact of radiation on rapidly proliferating cancers versus both acutely responsive and late-responsive normal tissues. In 1922, Henri Coutard presented findings that demonstrated a 23% success rate in the treatment of laryngeal cancer using fractionated external beam radiotherapy. This therapeutic approach involved the targeted delivery of X-rays to the tumor location from an external source, yielding significant outcomes without any detrimental consequences. These results were considered groundbreaking within the medical community during that era.

The effectiveness of external beam radiotherapy has been constrained by the utilization of low-energy photons. These photons possess the drawback of delivering a concentrated dose of radiation to the epidermis, while lacking the ability to penetrate tissue beyond a few millimeters. Following the conclusion of World War II, cobalt-60 emerged as a viable source of high-energy photon radiation, thereby facilitating the treatment of deep-seated cancers, marking a significant milestone in medical history. Additionally, it should be noted that cobalt-60-based radiotherapy has a differential radiation distribution, wherein the skin receives a lower dosage compared to the underlying tissues. The advent of linear accelerators facilitated the enhanced penetration of radiation into bodily tissues.

During the 1980s, there was significant progress made in the field of radiation therapy with the introduction of 2D-dose calculations. This advancement allowed for more precise planning of the radiation dose that was administered to various organs and tissues within the body. Subsequently, during the 1990s, the incorporation of CT scans into radiotherapy procedures and the utilization of 3D-dose calculation algorithms resulted in the development of 3D conformal radiotherapy. This advancement facilitated the creation of dose–volume histograms, which provided valuable insights into the correlation between radiation dosage and tissue responses. The aforementioned progress led to the formulation of mathematical models pertaining to the chance of complications in normal tissue and the probability of tumor control.

The utilization of precise imaging techniques has facilitated the implementation of stereotactic radiotherapy, a treatment modality that employs numerous small, high-energy beams originating from various angles to accurately focus on localized locations throughout the body. This approach has demonstrated exceptional efficacy in cancer reduction while exhibiting minimal incidence of adverse effects. Since the turn of the millennium, 4D scans have been employed to consider the potential presence of cancer mobility as well as the movement of healthy organs. In addition, the advancement of cone-beam computed tomography (CT) scans has facilitated the customization of radiotherapy treatments based on evolving anatomical conditions. This progress has effectively translated into the practical implementation of image-guided radiotherapy (IGRT) and dose-guided radiotherapy (DGRT) in clinical settings. Therefore, the utilization of intensity-modulated radiotherapy (IMRT) has become prevalent, as it enables the administration of reduced radiation doses to healthy tissues, thereby minimizing the occurrence of detrimental side effects. The incorporation of magnetic resonance imaging (MRI) scans into linear accelerators and proton treatment, with other advancements in technology, will enhance the accuracy and effectiveness of radiation therapy. Simultaneously, the advancements in molecular biology pertaining to radiotherapy, including its significant modulatory impacts and synergistic interactions with immune therapy, are propelling the progress of radiotherapy beyond its present state.

3. Newer technical developments in radiotherapy

3.1 Intensity-modulated radiotherapy (IMRT) is a type of three-dimensional radiotherapy, often known as 3D radiotherapy, use computer-generated graphics to visually represent the dimensions and contours of a cancer. Multiple radiation beams with varying intensity are directed onto the cancer from various angles. This particular form of radiotherapy minimizes the adverse effects on adjacent healthy tissue in close proximity to the tumor.

3.2 Image-guided radiation (IGRT) is a technique that utilizes medical imaging to enhance the precision and accuracy of radiotherapy treatment. The composition of an image involves the integration of the tumor and the surrounding anatomical structures, achieved by the use of cone-beam CT scans. These scans are acquired during the patient's preparation for radiotherapy administration, facilitated by a linear particle accelerator. The fusion of the original planned CT scan with the picture is observed, and the administration of irradiation occurs when the disparity between the two CT scans is either absent or falls within predefined limitations.

3.3 Dose-guided radiotherapy (DGRT) is a technique utilized in the field of radiation therapy. This technique, akin to Image-Guided Radiation Therapy (IGRT), utilizes cone-beam CT images acquired by a linear particle accelerator. The radiation dosage administered to the tumor and critical organs is computed and compared to the prescribed dosage. Irradiation is administered solely when the disparity is either absent or falls within predefined limits.

3.4 The Deep Inspirational Breath Hold (DIBH) technique involves patients taking a deep breath and maintaining it throughout the duration of radiation treatment. This action results in the lungs being filled with air and the heart being displaced from the chest. Deep inspiration breath-hold (DIBH) has demonstrated its utility in the field of radiotherapy for chest-related conditions, namely in reducing the radiation exposure to the heart. This technique has been effective in the treatment of left-sided breast cancer and mediastinal lymphoma.

3.5 Proton therapy is a form of radiation therapy that utilizes protons, which are positively charged particles, to treat cancer. Proton therapy is a form of radiotherapy that use protons as opposed to conventional photons. The utilization of proton therapy has the potential to decrease the amount of radiation received by healthy tissues, hence offering significant advantages in the treatment of several cancers affecting the head, neck, and organs such as the brain, eye, lung, spine, and prostate.

3.6 The MRI-linac system This apparatus integrates the utilisation of continuous magnetic resonance imaging (MRI) with the concurrent administration of radiation. Magnetic Resonance Imaging (MRI) is a modality that exhibits significant utility in specific anatomical regions, notably the brain and pelvis, due to its exceptional capacity for distinguishing soft tissues with heightened contrast.

4. The therapeutic index of radiotherapy

The parameter denoting the relative impact on tumor tissue compared to normal tissues, commonly referred to as organs at risk, is defined as the therapeutic index. The therapeutic index of radiotherapy can be characterized as a sigmoidal correlation between the dosage administered and the impact on both normal tissues and tumors. The disparity between the two curves is utilized to quantify the therapeutic index, as depicted in the accompanying image. Biological and physical techniques have the potential to enhance the therapeutic index. From a biological standpoint, the administration of low, frequent doses of radiation has been observed to result in a higher rate of cancer cell death compared to late-reacting cells, including endothelial cells and fibroblasts. This approach typically involves daily radiation doses. The irreversible nature of adverse effects on late-reacting tissues necessitates the limitation of radiation dose to prevent the occurrence of such consequences. The administration of a substantial cumulative radiation dose through multiple small fractions effectively mitigates the occurrence of unintended harmful effects in healthy tissues that are sensitive to radiation and exhibit delayed reactions1. The therapeutic index of radiation is considered favorable when the reaction of the cancer tissue surpasses that of the surrounding normal tissue, while also ensuring the prevention of serious consequences in the normal tissue. Optimized procedures are capable of delivering a significantly higher radiation dosage to the tumor while minimizing the radiation exposure to organs at danger. In addition, the utilization of radio protectors and mitigators, as well as specific tumor radio sensitizers, has the potential to enhance the therapeutic index. Stuschke, M. & Pottgen, C. (2010), Bernier, J., Hall, E. J. & Giaccia (2004), Giaccia, A. J. (2014), Moding, E. J. et, al. 2016. At present, the enhancement of cancer sensitivity to radiation is predominantly accomplished through the integration of radiotherapy with chemotherapeutic agents.

5. Physiological risks of radiation treatment in various cancers

Radiotherapy plays a significant role in the treatment of cancer, since it is utilised in around 50% of cases across diverse cancer types. Figure 1 illustrates the global distribution of cancer prevalence and the corresponding accessibility of radiation centres, as reported by the Directory of radiation Centres (DIRAC) dataset. Developing nations exhibit a substantial population size, yet demonstrate a comparatively limited presence of radiotherapy facilities in comparison to their industrialised counterparts.

5.1 Breast cancer

The therapeutic approach for breast cancer encompasses external beam radiation therapy (EBRT) as well as internal beam radiation therapy (IBRT). exterior beam radiation therapy (EBRT) is the targeted delivery of X-rays to the exterior surface of the malignant body for a short duration. On the other hand, intraoperative breast radiation therapy (IBRT) is a form of partial breast radiation that is associated with minimal adverse effects. Internal beam radiation therapy, also known as brachytherapy, involves the placement of a radio-active implant in close proximity to the tumour. A radiation dosage ranging from 4500 to 5000 cGy is administered over a period of five weeks as a therapeutic measure for malignancies located in the breast and lymph node regions. Dayes et al. (2006) advocate administering an additional dosage of 1000-2000 Gy over the course of one week as a boost.The administration of the whole dose does not occur in a single instance, but rather, it is divided into multiple daily doses referred to as "fractions." Typically, the initiation of radiation therapy occurs within a timeframe of around 3 to 4 weeks subsequent to surgical

intervention. Radiation therapy for breast cancer may result in several commonly observed side effects, including breast swelling and heaviness, fatigue, skin irritation in the treated area, which can range from mild to severe, and discoloration or a bruised appearance (Harris, Lippman, Morrow, & Osborne, 2014). Additionally, there may be complications related to breastfeeding, such as difficulties in lactation, as well as the development of lymphedema, acute radiation dermatitis, and a rare form of cancer known as angiosarcoma (Haruna, Lipsett, & Marignol, 2017).

5.2 Head and neck cancer

The primary procedures employed in the treatment of head and neck cancer are intensity-modulated radiation (IMRT) and brachytherapy. Intensity-modulated radiotherapy (IMRT) is an advanced technique derived from three-dimensional conformal radiation therapy (3D-CRT). IMRT allows for precise modulation of radiation intensity specifically at the targeted area, while minimising harm to adjacent healthy tissues (Eisbruch, Ten Haken, Kim, Marsh, & Ship, 1999; Nutting, Dearnaley, & Webb, 2000). There are two types of brachytherapy: intracavitary, which involves the placement of an implant within a cavity, and interstitial radiation, which involves the placement of an implant within or near a cavity that is not a body cavity. It is recommended to administer a dosage range of 56-70 Gy in the initial stages of head and neck cancer. The administration of 2 Gy per cent on a daily basis for a duration of 6 weeks is a viable approach. The dosage of radiation can range from 56 to 66 Gy, depending on the specific type of radiation (Pradier et al., 2004). The potential adverse effects of this medication include dysphagia, discomfort, alopecia, and dental caries. According to Bjordal, Kaasa, and Mastekaasa (1994), xerostomia, a dental disorder characterised by reduced saliva production, can result in several negative consequences. These include degraded oral hygiene, changed taste perception, nutritional deficiencies, poor sleep quality, and impaired speech function. According to Yeh (2010), the administration of a dosage of 35 Gy is associated with irreversible impairment of salivary gland function, resulting in the condition known as xerostomia.

5.3 Liver cancer

External beam radiation treatment, three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and stereotactic body radiation therapy (SBRT) have emerged as contemporary radiotherapy modalities for the management of liver cancer. Stereotactic body radiation therapy (SBRT) involves the precise administration of elevated radiation doses to a specific target area, while minimising harm to the adjacent healthy tissues. The technique known as three-dimensional conformal radiation therapy (3D-CRT) involves the administration of radiation beams in several tiny volumes that are specifically directed towards the three-dimensional shape of the tumour (Dawson et al., 2000). These approaches also exhibit numerous adverse effects. The radiation therapy dosage administered for liver cancer typically approximates 70 Gy. According to Fuss, Salter, Herman, and Thomas Jr (2004), the administration of radiation therapy doses ranging from 30 to 33 Gy to the entire liver is associated with a 5% risk of radiation-induced liver disease (RILD). However, an increase in dose to 40 Gy results in a significantly higher risk of RILD, with a 50% probability. The literature suggests that common adverse effects of the treatment include symptoms such as nausea, vomiting, gastritis, upper abdominal pain, gastric or duodenal haemorrhage, and fatigue (Dawson et al., 2000; Lawremce et al., 1991; McGinn et al., 1998; Rob-ertson et al., 1993).

5.4 Non-melanoma skin cancer

The treatment options commonly employed for non-melanoma skin cancer encompass external beam radiation therapy (EBRT), brachytherapy, and superficial radiation therapy (SRT) (Rong, Zuo, Shang, & Bazan, 2015). A cumulative radiation dose of 45 Gy is administered in 3 Gy fractions over a span of 15 treatment sessions, carried out over a duration of 3 weeks. During the course of treatment, individuals may exhibit erythema and experience minor discomfort. However, it is important to note that systemic adverse effects are seldom occurrences. According to McGregor, Minni, and Herold (2015), late consequences observed include hyper- or hypopigmentation, telangiectasias, and atrophy.

5.5 Thyroid cancer

Thyroid cancer is commonly managed with the application of external beam radiation therapy (EBRT) at a standardised dosage of 60 Gy administered over a course of 30 fractions (Brierley, 2011). Radioactive iodine therapy, often known as radioiodine or iodine-131, is employed for the purpose of identifying and eradicating residual thyroid cells that remain following surgical intervention. Some of the reported side effects include swelling or soreness of the salivary gland, headache, vertigo, sleeplessness, vocal cord paralysis, weariness, general malaise, foreign body sensation, body numbness, and signs of urinary tract infection (Lu, Shan, Li, & Lu, 2016).

5.6 Colorectal cancer

In the context of colorectal cancer, external beam radiation therapy (EBRT) is widely acknowledged as a viable and efficacious therapeutic option for patients diagnosed with stage IV disease. According to Bae et al. (2011), the administration of radiation therapy to colorectal patients involves a dosage range of 40 to 74 Gy, with each portion consisting of 1.8 to 2.0 Gy. Potential adverse effects may encompass symptoms such as nausea, bowel incontinence or leakage of stool, exhaustion, tiredness, rectal irritation, skin irritation, bladder irritation accompanied by a burning feeling or pain during urination, diarrhoea, painful bowel movements, and presence of blood in the stool. In addition, it has been observed that radiation therapy might lead to sexual complications, such as vaginal irritation in women and erectile dysfunction in males (Van Schaeybroeck et al., 2005).

5.7 Prostate cancer

The most commonly employed technique for detecting lymph nodes and metastases in cases of prostate cancer is positron emission tomography (PET) using prostate-specific membrane antigen (PSMA)-based external beam radiation therapy (EBRT). This technique is known for its high specificity and sensitivity. The administration of external beam radiation therapy to individuals with prostate cancer has been found to lead to the emergence of obstructive voiding symptoms, hence exerting a detrimental impact on their overall quality of life (Hoppe et al., 2014; Sanda et al., 2008). Prostate cancer at the initial stage can be treated using a radiation dosage of 70.2 Gy or an escalated dosage of 79.2 Gy. The administration of a booster dose ranging from 19.8 to 28.8 Gy might be conducted subsequent to surgical intervention or during the latter stages of malignancy. The potential adverse effects encompass radiation proctitis, rectal bleeding, diarrhoea, hematochezia, radiation cystitis, impotence, fatigue, lymphedema, and erectile dysfunction (Vicini, Kestin, Ghilezan, & Martinez, 2006; Zietman et al., 2005).

5.8 Lung cancer

The treatment of lung cancer encompasses two modalities of external beam radiation therapy (EBRT), namely three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT). Despite the occurrence of specific adverse effects, a normal dosage of 60 Gy of radiation therapy (RT) is administered in 4-5 fractions for the treatment of lung cancer (Ming et al., 2016). An increase in dosage to 70 Gy is associated with significant risks, including symptoms such as shortness of breath, difficulty in swallowing, shoulder stiffness, cough, fever, breast or nipple soreness, and the development of radiation pneumonitis. These adverse effects can manifest within a timeframe ranging from 2 weeks to 6 months following radiotherapy and have been shown to negatively impact survival rates (Gensheimer & Loo, 2017).

5.9 Endometrial cancer

Commonly employed therapies for endometrial cancer encompass adjuvant vaginal brachytherapy and pelvic external beam radiation therapy (EBRT). Early stage endometrial cancer can be effectively treated by administering a total dosage of 46 Gy, which can be provided over a course of 23 fractions spanning a period of 5 days per week. Furthermore, medical professionals advise administering an additional dose ranging from 1000 to 2000 Gy as a supplementary dosage over the course of one week. Bowel incontinence, rectal haemorrhage, bladder irritation, and diarrhoea are frequently observed adverse effects, often accompanied by alterations in menstruation, vaginal pruritus, burning sensation, dryness, and impaired fertility (Kellas-Sleczka, Wojcieszek, & Białas, 2012).

5.10 Ovarian cancer

In the context of ovarian cancer, various types of radiation therapy (RT) are employed based on the stage of the disease. These include adjuvant RT for early-stage cases, consolidative RT for advanced-stage cases, salvage RT for recurring disease, and palliative RT for cases with metastatic disease. The abdomen region is subjected to a cumulative dosage ranging from 22.5 to 33 Gy, divided into 10 to 24 parts over a period of 5 weeks. In addition, an extra dosage of 40 to 45 Gy is supplied specifically to the pelvis. The radiation therapy regimen for epithelial ovarian cancer typically involves external beam radiation therapy (EBRT) administered to the entire abdominal cavity. This treatment is delivered in 22-24 fractions, with a total dose of 22-24 Gy. Subsequently, radiation is targeted specifically to the pelvis, with a dose of 23.4-21.6 Gy administered in 12-13 fractions. According to Rai, Bansal, Patel, and Sharma (2014), various adverse effects were observed, including radiation entero-colitis, intestinal discomfort, and vaginal irritation.

6. Genetic mutations occurring after radiation therapy in cancer patients

Chromosomal aberrations are a significant unfavourable consequence induced by radiation therapy in individuals diagnosed with cancer. Cancer patients who have had radiation therapy exhibit structural chromosomal abnormalities as well as numerical or copy number alterations (Grade, Difilippantonio, & Camps, 2015). The occurrence of cancer can be attributed to genetic mutations that have affected the genes responsible for cell proliferation and cellular repair, leading to their accumulation in the genome (Kim, Chandrasekaran, & Morgan, 2006; Klein, Casey, & Silverman, 2006; Sandberg, 1991). According to Sprung et al. (2005), there is a direct correlation between the radiation dose and the change in frequency of chromosomal aberrations. The dicentric chromosome, characterised by the presence of two centromeres or translocated chromosomes, poses a potential risk of radiation exposure, as determined through the assessment of chromosomal abnormalities (Abe et al., 2016). Dicentric chromosomes exhibit instability in cells, rendering them incapable of undergoing repeated mitotic division. However, the translocated chromosomes remain stable. The production of dicentric chromosomes and translocations in human peripheral blood is observed to be equivalent following radiation therapy, as reported by Kanda (1996) and Zhang and Hayata (2003). Radiation therapy induces the generation of free radicals within cells, which subsequently leads to the occurrence of DNA breakage, change of base pairs, and cross-linking between DNA strands. The detrimental impact of radiation generally results in genetic abnormalities during the process of DNA replication and disrupts the DNA repair mechanism (Lori-more & Wright, 2003). Recent research indicates that the transmission and expression of mutations resulting from radiation therapy in cellular DNA can occur in the surviving offspring cells (Tomita & Maeda, 2015). The occurrence of genomic instability is associated with the radiation-induced bystander effect, leading to various consequences such as DNA damage, chromosomal instability, mutation, and apoptosis (Kadhim et al., 2013; Kaplan, Limoli, & Morgan, 1997; Little, 2003; Morgan, Day, Kaplan, McGhee, & Limoli, 1996). Prolonged exposure to a minimal amount of radiation can also result in chromosomal abnormalities, such as aneuploidy, gene loss, and stable and unstable aberrations (Cho et al., 2015; Heim, Lench, & Swift, 1992; Kadhim et al., 1992; Little, 2003). The prevalent kind of genetic abnormality is aneuploidy, which arises from errors in the segregation of chromosomes during mitosis (Malmanche, Maia, & Sunkel, 2006), (Sen, 2000).

7. Secondary malignancies after radiation therapy

Secondary malignancies, often known as secondary cancers, are neoplastic diseases that manifest subsequent to the completion of primary cancer treatment. According to Lin (2016), the utilisation of radiotherapy, either alone or in conjunction with chemotherapy, presents a possible risk factor for the development of secondary cancers. While ionising radiations are employed for the purpose of eradicating cancerous tissues, there is a notable occurrence of second malignant neoplasms (SMNs) among individuals who have survived for an extended period of time. Therefore, ionising radiations are recognised as carcinogenic agents. The rise in survival rates has led to a growing worry among long-term survivors regarding the increased risk of secondary malignant neoplasms (SMN) associated with radiation therapy (de Gonzalez et al., 2011; Tubiana, 2009; Xi et al., 2013). Early detection of recurrent cancers is crucial in order to minimise morbidity and improve overall survival rates (Benveniste et al., 2013). The impact of radiotherapy and the tumour microenvironment on "naïve" cells and tissues involves the stimulation of inflammatory agents, including cytokines and free radicals. Subsequently, the activated immune system elicits oxidative DNA damage either directly or indirectly within the surrounding milieu. Hence, the timely monitoring of DNA damage facilitates the comprehension of the fundamental mechanisms behind non-targeted effects (Sprung et al., 2015). Radiation therapy-induced cancer manifests three distinct distinctive traits. The histological characteristics of primary and secondary tumours exhibit notable distinctions. Furthermore, the occurrence of secondary cancers has been observed in the region that has had prior radiation therapy. Moreover, secondary cancer exhibits a latency period of five years. The fundamental aetiology of secondary malignancy is attributed to the occurrence of DNA damage during the therapeutic intervention for the first neoplastic condition. The likelihood of secondary malignancy recurrence is significantly diminished in those diagnosed with breast cancer. The incidence of secondary malignancies resulting from radiotherapy is rather low in comparison to other factors such as lifestyle choices, exposure to carcinogens, and genetic predisposition (de Gonzalez et al., 2011).

8. Infertility after radiation therapy

Fertility complications may arise in women who undergo radiation therapy in the abdominal or pelvic region, depending on the administered dosage. The administration of a high dosage of radiation therapy results in the depletion of oocytes within the ovarian follicles, consequently inducing premature ovarian failure and the onset of menopause at an earlier age. Although exposure to RT can lead to reduced fertility in women, it is important to consider that the specific site of exposure may also influence future reproductive outcomes. According to Cruz and Bellver (2014), the administration of abdominopelvic radiation therapy has been associated with many adverse outcomes, including

miscarriage, preterm labour, low birth weight, and placental abnormalities. When radiation is administered to the uterus as a treatment for endometrial cancer, the ovaries are exposed to a significant amount of radiation. This exposure has been found to result in a 5% infertility rate, as well as various side effects including miscarriage, low birth weight in infants, and premature birth (Balcerek, Reinmuth, Hohmann, Keil, & Borgmann-Staudt, 2012; Gnoth et al., 2005; Habbema et al., 2009; Wo & Viswanathan, 2009). The impact of radiation on the brain has been observed to have consequences on the functioning of the pituitary gland, thus leading to alterations in hormonal balance and afterwards affecting the pace of ovulation. The reproductive rate is determined by the dosage and extent of exposure. Craniospinal irradiation induces hormonal alterations that may give rise to potential complications associated with pregnancy at later stages of life. Cranial irradiation has been found to induce malfunction within the hypothalamic-pituitary axis, resulting in adverse effects such as uterine injury or aberrant ovulation. According to Ash (1980), people who have received cerebral irradiation experience abnormalities in their gonadal axis. There exists a correlation between the dosage of radiation administered and the age of patients. As an illustration, it has been observed that a radiation dose of 400 cGy leads to a 30% incidence of infertility among young women. Conversely, the identical dose results in complete sterility, reaching 100%, among women aged 40 years and above.

In the male population, it has been observed that fractionated irradiation of the testes may potentially provide a greater risk compared to acute irradiation, particularly when the cumulative dosage does not exceed 600 cGy. According to Grover et al. (2012) and Zaletel, Todorovski, and Jereb (2012), it has been observed that a fractionated dosage (FD) exceeding 35 cGy leads to the condition of aspermia. The duration of recovery from this condition is dependent on the dosage administered. However, if the FD surpasses 200 cGy, there is a significantly elevated likelihood of experiencing aspermia. The occurrence of primary testicular injury is observed when radiation is specifically targeted in close proximity to the testicles. Spermatogonia exhibit a higher degree of sensitivity towards radiation exposure. Even a dosage as low as 600 centigray (cGy) induces irreparable harm, although doses lower than this threshold result in a decrease in both the quantity and quality of sperm production. Secondary or indirect testicular failure may manifest as a result of radiation therapy (RT) administered to the brain. This phenomenon leads to harm inflicted upon the pituitary gland, leading to a disruption in the equilibrium of hormones, namely follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Both of these hormones play a crucial role in the stimulation of spermato-gonia and Leydig cells. Additionally, this will result in a reduction in the synthesis of testosterone. During the surgical procedure known as prostatectomy, the prostate gland and the adjacent seminal vesicles are surgically excised. In conjunction with the prostate gland, these structures facilitate the transportation of sperm into the urethra, ultimately leading to their expulsion from the penis during the process of ejaculation. Radiation therapy-induced damage results in a condition known as ejaculatory dysfunction, rendering ejaculation unattainable. Consequently, the spermatozoa are unable to exit the body and subsequently fail to reach the ovum, thereby impeding the process of fertilisation (Orth et al., 2014). Individuals who undergo larger doses of radiation therapy and chemotherapy experience a prolonged delay in the restoration of sperm production. Various factors, including preexisting fertility conditions and advanced maternal age, can exert an influence on an individual's reproductive capacity. The impact of exposure to RT on sperm production in pre-pubertal males is minimal, with limited reduction observed. However, more intensive treatment regimens have been found to lead to early sterility. Leydig cells have a notable degree of resilience towards the deleterious impact of radiation therapy (RT). According to Nutting et al. (2001), Leydig cells exhibit normal functioning when exposed to levels below 2400 cGy. These cells are responsible for the production of testosterone, a hormone essential for maintaining regular sexual activity.

9. Recent treatment strategies in radiotherapy

In contemporary oncology, the prevailing methods for cancer treatment encompass intensity-modulated radiation (IMRT) and image-guided radiotherapy (IGRT) (Nutting et al., 2001). The use of intensity-modulated radiation therapy (IMRT) technology has been proposed as a means to enhance target coverage while minimising damage to adjacent cells. Several studies (Bortfeld, 1999; Chandra et al., 2005; Kole, Aghayere, Kwah, Yorke, & Goodman, 2012; Nguyen et al., 2012) have demonstrated that contemporary radiotherapy techniques exhibit reduced toxicity compared to traditional radiotherapy techniques. Image-guided radiotherapy (IGRT) is a form of radiation therapy that utilises X-rays to deliver treatment. This technique involves the scanning of the tumour site, enabling the radiotherapy field to encompass both the tumour location and its surrounding border. This diagnostic technique provides information regarding the dimensions, morphology, and spatial orientation of malignant cells, as well as the adjacent tissue structures. According to Lin et al. (2012), the utilisation of intensity-modulated radiation and image-guided radiotherapy in the treatment of locally advanced esophageal cancer has been found to result in both curative outcomes and acceptable complications, without exacerbating any pre-existing detrimental consequences. The utilisation of variations in intensity-modulated radiation therapy (IMRT) treatment aims to achieve optimal control

while minimising the potential harm to adjacent cells. In the context of intricate therapeutic interventions such as distal esophageal cancer, the utilisation of intensity-modulated radiation therapy (IMRT) has been found to yield superior outcomes compared to three-dimensional conformal radiation therapy (3D-CRT) (Bujold, Craig, Jaffray, & Dawson, 2012; Dolezel et al., 2015). Therefore, novel techniques such as Intensity-Modulated Radiation Therapy (IMRT) and Image-Guided Radiation Therapy (IGRT) have emerged as improved treatment modalities with reduced incidence of adverse effects. Intensity-modulated radiation (IMRT) has the capability to administer high-dose gradients, hence possessing significant clinical implications. Additionally, this technique enhances the precision of intensity-modulated radiation therapy (IMRT) while minimising potential injury to adjacent tissues. Image-guided radiotherapy (IGRT) serves as a means of ensuring the quality of high-quality intensity-modulated radiation treatment (IMRT) (Grills et al., 2008). Additionally, the utilisation of IMRT in conjunction with three-dimensional conformal radiation therapy (3D-CRT) enhances the precision of target localization and mitigates the potential occurrence of myelopathy. Intensity-modulated radiotherapy (IMRT) is a treatment strategy that not only minimises radiation exposure to organs at risk, but also allows for the delivery of varying radiation doses to distinct tumours. This approach is generally referred to as the simultaneous integrated boost technique (De Ruysscher et al., 2010). In recent years, advancements in technology have led to a decrease in planning target volume margins. These advancements include the utilisation of cone beam computed tomography (CBCT) and 4D-CT modelling (San-gro, Iñarrairaegui, & Bilbao, 2012). According to Yu and Kim (2015), the utilisation of intensity-modulated radiation therapy (IMRT) and proton beam therapy (PBT) approaches has yielded more precise calculations in a clinical setting. The emergence of carbon-ion radiotherapy (CIRT) is considered to have significant value due to its ability to deliver a sufficient volume of radiation to the tumour site while minimising the dose to surrounding normal tissues. This is achieved through the use of carbon ions, which possess a higher atomic mass and can effectively penetrate into the tumour, resulting in improved treatment outcomes compared to other particles (Tsujii, 2017). The procedure known as transarterial radioembolization (TARE) involves the utilisation of a high-energy radioisotope, specifically yttrium 90 (Y), which emits pure beta rays. These rays are encapsulated within microspheres ranging in size from 25 to 32.5 μM. Subsequently, these microspheres are introduced into tumours (Kennedy et al., 2007; Liapi & Geschwind, 2010). According to several studies (Lau et al., 2013; Sato et al., 2006), transarterial radioembolization has been found to result in reduced circulatory system damage. This is achieved by the process of microembolization, which involves minimum to moderate levels of embolisation (Budach, Hehr, Budach, Belka, & Dietz, 2006; Orth et al., 2014; Salem et al., 2010). There is evidence to suggest that the application of stereotactic ablative radiation (SABR) in the treatment of non-small cell lung cancer (NSCLC) among elderly individuals yields positive outcomes. In Stereotactic Ablative Radiotherapy (SABR), the radiation beams converge at distinct locations within the tumour, thereby facilitating the delivery of radiation with optimal intensity to the targeted site. Therefore, the tumour is exposed to a concentrated and intense radiation dosage within a limited spatial extent. The utilisation of chemotherapy in conjunction with radiotherapy has demonstrated significant success in the management of cancer (Begg, Stewart, & Vens, 2011). In addition to this, the utilisation of a combination therapy involving radiotherapy and molecularly engineered medicines that selectively target cancer cells has been shown to yield improved treatment outcomes. The stratification of patients is expected to have a positive impact on the efficacy of this particular technique, leading to a reduction in associated side effects (Niyazi et al., 2011). The introduction of smart radiotherapy biomaterials (SRBs), namely radio-opaque fiducial markers, into the tumor-bearing organs can potentially mitigate the adverse effects on adjacent cells. The markers utilised in this context are composed of radio-opaque substances, such as gold or a metal alloy, which serve the purpose of identifying the location of the tumour. One notable benefit of employing this particular approach lies in its capacity to exhibit low levels of immunogenicity and toxicity, as highlighted by Bair, Bair, and Vis-wanathan (2015). Another radiation approach that can be utilised is the Rapi-dArc technique, also known as volumetric modulated arc treatment (VMAT). This technique allows for the delivery of a highly conformal dose distribution by completing a full rotation of approximately 360°. When comparing VMAT to conventional radiation therapy and IMRT, several studies (Clivio et al., 2009; Cozzi et al., 2008; Palma et al., 2008; Shaffer et al., 2010; Verbakel et al., 2009) have found that VMAT offers improved accuracy and reduced harm to surrounding tissue, providing a distinct advantage. Volumetric modulated arc treatment (VMAT) is an advanced iteration of intensity-modulated radiation therapy (IMRT). The methodology known as VMAT is now being developed as a clinical therapeutic method. However, it is important to note that VMAT is not a universally curative approach for all clinical problems (Holt, van Vliet-Vroegindeweij, Mans, Belderbos, & Damen, 2011). Nonetheless, VMAT does have a significant impact on enhancing the quality of life for patients.

10. Fortification of risks of radiotherapy

According to Lu et al. (2016), the utilisation of radiosensitizers and radioprotectors can effectively mitigate the negative consequences associated with radiation therapy (RT). Radiosensitizers refer to chemicals that possess the ability to sensitise the intended tumour target, hence facilitating the elimination of free radicals generated as a result of cellular damage. Hyperbaric oxygen, car-bogen, nicotinamide, metronidazole, hypoxic cell cyto-toxic chemicals such as mitomycin-c, tirapazamine, motexafin gadolinium, taxanes, and irinotecan are among the radiosensitizers employed to enhance the effectiveness of radiation therapy treatment. Radioprotectors primarily consist of antioxidants that can be administered prior to or concurrently with radiation therapy (RT) in order to safeguard normal cells. Amifostine (Ethyol) and nitroxides are two instances of radioprotectors, as mentioned in studies conducted by Prasanna et al. (2015) and Raviraj, Bokkasam, Kumar, Reddy, and Suman (2014).

The efficacy of Ayurvedic radioprotectors, which have been found to have no discernible negative effects, has garnered significant attention and interest among researchers and therapists. Numerous current preclinical and clinical investigations are being conducted to explore the radioprotective properties exhibited by various plant species. Previous research has indicated that various ayurvedic formulations, including Tri-phala, Amritaprasham, Chyavanprasha, Ashwagandha Rasayana, Brahma Rasayana, and Narasimha Rasayana, possess radioprotective properties. These formulations have been found to scavenge free radicals, reduce oxidative stress, prevent DNA damage, promote the regeneration of bone marrow progenitors, provide anti-inflammatory chemoprotection, and exhibit immunomodulatory effects (Baliga, Meera, Vaishnav, Rao, & Palatty, 2013).

11. Conclusions

The advancement of science and technology has led to the emergence of novel methodologies that enhance the efficacy of cancer treatment. Within the realm of radiation therapy, there exists a range of methodologies, some of which have already been implemented in practise, while others necessitate further investigation before they can be widely adopted. Despite the emergence of novel therapeutic approaches for cancer treatment, radiation therapy (RT) continues to play a crucial role in the management and control of a wide range of cancer types. Furthermore, it serves a crucial function as a technique for preserving organs, hence diminishing the necessity and likelihood of surgical intervention. Particularly, the utilisation of ayurvedic medications in conjunction with radiotherapy has been discovered to offer enhanced treatment outcomes.

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