Chapter 22

Current Status of Organoprotective Agents and Strategies Against the Adverse Effects of Radiotherapy on the Genital Systems

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Abstract

Radiotherapy is one of the most commonly used therapeutic methods in cancer treatment. Despite the increasing survival rates and durations due to the advancements in treatment technologies for cancer, the number of diagnosed cancer cases is on the rise annually, driven by environmental changes such as physiological aging, environmental pollution, increased carcinogen exposure, and disturbances in the ozone layer. While the advancements in medical science have brought promising results in cancer treatment through genetic engineering and molecular regulation methods, every new technology also leads to the emergence of both side effects and losses alongside its benefits. Leaving aside the emerging technological innovations, the most frequently utilized clinical approaches in cancer treatment involve the integration of the subfields of Medical Oncology and Radiation Oncology, as well as Oncological Surgical approaches. Radiation Oncology is a medical science aimed at extending survival or completely curing the patient by using ionizing radiation to treat cancer. The primitive therapeutic method employed in Radiation Oncology is radiotherapy, and the ionizing radiation used in this classical treatment method can have adverse effects not only on the targeted tumor organs/tissues but also on healthy organs or tissues. Despite the advancement

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of radiotherapy technology and the development of more modern targeting techniques, conventional gamma radiotherapy applications are still widely used today. Although scientists have developed some strategies in recent years to alleviate healthy tissue damage and side effects caused by radiotherapy, a definitive protective solution has not yet been found. One of the systems where organ dysfunction and systemic abnormalities due to radiotherapy are most commonly observed is the reproductive system. This book chapter will discuss the current status of radioprotective agents, which are scientifically promising and used today to prevent female and male reproductive system anomalies during radiotherapy applications using gamma rays.

1. Introduction to the Radiotherapy-Induced Organ Injury

Radiation or radiotherapy-induced organ damage is a process that leads to reversible or permanent injury and organ dysfunction in nearby or distant organs outside the targeted tumor area, limiting the usability of radiotherapy in cancer treatment [1]. Due to the fundamental principles of radiotherapy, the choice of radiation method cannot be arbitrary. Ionizing radiation is used to ionize atoms and molecules, break chemical bonds, and eliminate transformed cells. Ionizing radiation directly damages cell DNA or proteins, and indirectly generates free radicals and reactive oxygen species (ROS), leading to destructive effects through the bystander effect, which can even affect tissues not directly exposed to radiation. Additionally, recent strong observations regarding the bystander effect on healthy tissues and organs in radiation oncology have the potential to limit the capabilities and applicability of this treatment method, which is one of the most commonly used in cancer therapy [2, 3].

One of the systems most intensely affected by the destructive effects of ionizing radiation from radiotherapy is the reproductive system, specifically the gonads [4]. While some methods have been developed in this area, no definitive protective strategy has yet been established. The problems arising after treatment are not limited to physical, physiological, and biological factors but also affect other parameters that directly impact the patient's quality of life. In this context, the approach to cancer treatment includes not only medical interventions targeting the disease but also supportive therapies, such as psychological support [5].

The term "oncofertility," introduced in 2006, emerged in response to the recognition of the psychological and quality-of-life impacts of fertility issues related to cancer treatment. This concept involves informing and managing patients about risks to reproductive health, hormonal imbalances, sexual dysfunction, and delayed puberty, among other potential complications

[6]. Radiotherapy-induced damage to the genital system, which may lead to temporary or permanent harm, has the potential to significantly affect a person's sexual health, psychology, and family life. While some treatment methods have been developed for restoring sexual and reproductive health or protecting against radiotoxicity, these methods remain limited, and scientific research in this area is ongoing.

1.1. Main Principles of Radiotherapy-Induced Infertility

Radiotherapy is one of the most commonly used treatment methods in cancer therapy. In some cases, it may even be the first treatment option offered to patients when deemed sufficient, and in certain cancer cases, it can be a clinical intervention that facilitates the completion of treatment. On the other hand, radiation exposure causes a gonadotoxic effect, which can result in ovarian insufficiency, disruption of puberty, or sterility in the long term. Following cranial irradiation for head and neck cancers, the hypothalamic-pituitary-gonadal axis, which is responsible for regulating the physiology of the genital system, may be disrupted, leading to hormonal imbalance and fertility issues [7]. Moreover, radiation exposure can cause direct damage to organs involved in the reproductive system, such as the uterus, ovaries, and testes, which play a role in pregnancy formation. As a consequence, subfertility and infertility can develop. In an experimental study, after radiotherapy applications were performed on rats, a significant increase in malondialdehyde (MDA) levels, a marker of oxidative stress, was observed in testicular tissue. This was accompanied by a dramatic decrease in glutathione (GSH) levels, a key component of the endogenous antioxidant mechanism [8]. In this experimental study by Topcu et al., histopathological degenerations were observed in the testes of animals subjected to both abdominopelvic and total body irradiation, with pathological conditions such as edema and pyknosis in the nuclei of spermatogenic cells. Additionally, the study found that reductions in testicular size and germinal epithelium thickness were important findings in understanding radiation-induced testicular dysfunction in individuals exposed to ionizing radiation. However, in another study on experimental animals, a significant increase in atretic follicle numbers was observed in ovaries as the radiation dose increased [9]. In this study, it was demonstrated that ionizing radiation led to a significant increase in the expression levels of apoptotic markers Bax and Caspase-3 in ovarian stromal and follicular cells, while the anti-apoptotic protein Bcl-2 showed a noticeable decrease. Önder et al.'s study also reported a visible increase in the levels of inflammatory cytokines expressed in the ovaries due to ionizing radiation exposure.

A review of existing studies in the literature shows that in nearly all of these studies, histological changes in reproductive organs due to ionizing radiation exposure have been observed. Disruptions in the balance of protein expression, which could lead to cell death or affect cell viability when compared to the overall homeostatic condition of the organ, have also been reported. Furthermore, taking into account the information available in the literature, it is evident that this condition can be mitigated or partially reversed using certain preservation methods.

1.2. Adverse Effects of Radiotherapy on the Female and Male Genital Systems

1.2.1. Radiation-Induced Female Reproductive System Disorders

1.2.1.1. Overview of the Female Genital System

The female genital system is responsible for reproduction, the transportation of the fetus until birth, and the synthesis of reproductive hormones. It is divided into two parts: the external and internal genital organs. The external genital organs include the mons pubis, labium majus, labium minus, hymen, perineum, clitoris, vestibulum vaginae, urethral orifice, and glandular structures (such as Skene and Bartholin glands). All of these external genital organs are collectively referred to as the vulva. The internal genital organs consist of a pair of ovaries, the fallopian tubes that carry the oocytes released from the ovaries, the uterus where the embryo implants and develops, and the cervix. These organs are located within the pelvic cavity, where estrogen and progesterone are synthesized by the ovaries, and ova are matured. Estrogen thickens the endometrium of the uterus and enriches it with blood vessels in preparation for embryo implantation. If fertilization occurs, progesterone supports continued development. If fertilization does not occur, the oocyte is expelled from the body along with blood, and menstruation occurs. As a result, a new menstrual cycle begins, marked by the development of new follicles, regulated by the hormones FSH and LH.

1.2.1.2. Radiation-Induced Female Genital Organ Troubles and Infertility

Radiation, present in many aspects of modern life, exerts toxic effects on human health depending on several factors (such as gender, age, radiation dose, etc.) [10]. Ionizing radiation used in radiotherapy can cause significant damage to cellular DNA and can potentially affect the entire organism. These damages can vary depending on the type of radiation, dose, and radiation

quality. Energy accumulation on DNA creates direct damage, interacting with free radicals and leading to erroneous DNA repair by enzymes [11, 12]. During radiotherapy, damage is not limited to the tumor but also affects nearby tissues. In addition to damaging nearby tissues, radiation disrupts hormonal homeostasis, negatively impacting reproductive hormones, fertility, libido, and the menstrual cycle [10]. A study found that radiotherapy applied to the ovarian outer area in the pelvic region resulted in secondary ovarian cancer. Both chemotherapy and radiotherapy affect female ovaries, impacting fertility potential, with the extent of damage varying according to factors such as the patient's age, chemotherapy regimen, and pelvic radiation dose [13, 14]. Chemotherapeutic agents used in conjunction with radiation may further increase the level of ovarian damage. Ovarian reserve tests are used to assess the degree of ovarian damage. These tests include the measurement of Anti-Müllerian hormone (AMH) levels, counting antral follicles via transvaginal ultrasound, and measuring estradiol (E2) and follicle-stimulating hormone (FSH) levels on day 3 of the menstrual cycle. Radiation exposure significantly reduces the number of oocytes, which can ultimately lead to sterility [10]. In pelvic radiotherapy, ionizing radiation not only damages the ovaries but also the vaginal epithelium. The damage to the vagina becomes apparent within the first 3 months, manifesting as erythema, inflammation, mucosal atrophy, loss of elasticity, and ulceration (wounds caused by tissue breakdown) in the vaginal tissue. As a result, a reduction in vaginal lubrication, dryness, and narrowing of the vaginal canal occurs, increasing the risk of infection and trauma [15].

As for the effects of radiotherapy on female genital internal organs, ionizing radiation causes ovarian insufficiency, pubertal arrest, and infertility, leading to the emergence of a gonadotoxic condition. Additionally, the uterus, which is the most muscular and solid structure of the female reproductive system, is also affected by the destructive properties of ionizing radiation. Radiation exposure during childhood alters uterine vascularization, reduces uterine volume and elasticity, leads to myometrial fibrosis and necrosis, and causes endometrial atrophy and insufficiency. Low doses of radiation can damage the inhibitory GABA system, resulting in early activation of GnRH neurons and causing early puberty in girls [10]. Furthermore, women who had cancer treatment during childhood are at a higher risk of high-risk pregnancies later in life and may have difficulty with normal childbirth due to prior radiation exposure. The DNA damage caused by radiation not only affects the individual's body but also significantly impacts gametogenesis and embryonic development. Radiation exposure increases the risk of miscarriage in adults. The integrity of DNA is crucial for conception, healthy

offspring, and embryonic development [10, 16]. Even a dose of less than 2 Gy of radiotherapy is sufficient to destroy half of the ovarian follicles [17].

1.2.1.3. Current Preservation Methods Used in Females

Several preservation methods have been developed to minimize radiation-induced damage to the female reproductive system. These methods are used to prevent or reduce the potential risks of infertility, hormonal disorders, follicle depletion, secondary cancers, radiation-induced damage to the offspring, and female genital organ damage [18]. Some of the preservation methods include:

1. Ovarian transposition
2. Embryo cryopreservation
3. Oocyte cryopreservation
4. Fertility counseling before treatment
5. Ovarian tissue cryopreservation, etc.

Furthermore, a study investigating the effects of radiotherapy on uterine tissue found that agents such as melatonin, amifostine (WR-2721), and N-acetylcysteine exhibited varying degrees of protective effects on uterine tissue. However, the protective effect of melatonin was found to be significantly more pronounced [19].

1.2.2. Radiation-Induced Male Reproductive System Disorders

1.2.2.1. Overview of the Male Genital System

The male genital system consists of a series of internal and external organs responsible for reproduction and urinary excretion. The external organs include the penis, which allows both urine and semen to pass through the urethral canal and performs functions such as erection and ejaculation. The scrotum, which is connected to the penis, serves as a protective sac for the testes, helping regulate temperature to support healthy sperm production. Located within the scrotum, the testes produce sperm cells and the male sex hormone, testosterone. Sperm cells produced in the testes are stored and mature in the epididymis. Mature sperm are transported to the prostate gland via the vas deferens. The prostate gland secretes fluid that supports sperm transport and maturation, and this fluid combines with secretions from the seminal vesicles, contributing to sperm formation. This fluid mixture is then expelled through the urethra, enabling reproduction.

1.2.2.2. Radiosensitivity of the Male Reproductive System and Its Relationship with Radiotherapy

As predicted by the Bergonié-Tribondeau principle, human male gonads are among the most radiosensitive tissues in the body, regardless of the patient's age. At the cellular level, spermatogonia (especially type B) exhibit the highest radiosensitivity, as they are the least mature components of the seminiferous tubules and are affected by doses as low as 0.1 Gy. Spermatocytes are affected by doses between 2-3 Gy, and spermatids by doses above 4 Gy. Sertoli cells are less affected than spermatogonia, showing resistance up to doses of 1.5 Gy. Leydig cells are more resistant to higher doses, with resistance levels of 20 Gy and 30 Gy for prepubertal and post-pubertal individuals, respectively [20, 21]. Due to their high radiosensitivity, testes are also affected by localized or total radiotherapy. The extent of the effect depends not only on the radiation dose but also on the fractionation scheme and the treatment area. Testicular irradiation, rectal irradiation, or pelvic radiotherapy can lead to damage, as well as total-body irradiation used in treatments for Hodgkin lymphoma, other lymphomas, and leukemia. Fractional radiotherapy targeting or including the testes is common in patients undergoing radiotherapy for diagnoses such as seminomas, acute lymphoblastic leukemia, lymphoma, and sarcoma. These treatments can produce well-known effects on both exocrine and endocrine testicular functions [20, 22-24]. In a study conducted by Speiser et al., 10 patients were treated with reverse Y inguinal irradiation for Hodgkin lymphoma, with doses of 1.2-3 Gy delivered in 14-26 fractions. The initial results showed that azoospermia occurred in all patients after treatment, and no signs of recovery were observed in four patients after 15 months and in one patient after 40 months. In updated analyses, permanent azoospermia was observed in patients who received doses higher than 1.4 Gy after 17-43 months of follow-up, while two patients who received a gonadal dose of 1.2 Gy regained fertility potential, indicating the existence of a threshold dose level below which irreversible testicular damage does not occur [20]. In addition to regional irradiation, total body irradiation (TBI), particularly used for bone marrow transplants, is associated with significant gonadal toxicity. Previous studies have shown that 99.5% of males who received 12.0 Gy of TBI (average age 31, range 11-62 years) experienced permanent infertility [24].

1.2.2.3. Mechanism of the Effect of Radiation on the Male Reproductive System

The gonadotoxic effects of radiotherapy are highly pronounced in germ cells, spermatozoa, the endocrine system, and the histological structure of the gonads, potentially leading to temporary or permanent infertility in males. The extent of gonadotoxic effects depends on the duration of exposure and the frequency of radiation. High-frequency radiation can alter cellular organelles, but the major damage occurs at the DNA level, which may result in cell death. DNA damage can occur through both direct and indirect ionization processes [25, 26]. According to biophysical principles, direct and indirect ionization can be defined as follows:

Direct Ionization: High-energy radiation directly interacts with the DNA molecule, liberating electrons from the DNA and resulting in DNA destruction.

Indirect Ionization: Radiation interacts not directly with DNA but with water molecules in the cell, causing ionization of the water molecules and the production of free radicals. These free radicals then disrupt the structural integrity of the DNA. Due to the abundance of water in the body, indirect ionization becomes a more common mechanism of damage than direct ionization [26].

Radiation, through these DNA damage pathways, can indirectly reduce sperm production by affecting germ cells or directly damage spermatozoa, leading to male infertility. In terms of sperm cell lineage, reactive oxygen species (ROS) production leads to various DNA lesions, including chromosome deletions, cross-linking between chromatins, and single or double-strand breaks. ROS further intensifies DNA strand breaks via the induction of apoptotic mediators such as cytochrome c, caspases 9 and 3. Additionally, ROS causes lipid peroxidation in the cell membrane, leading to DNA damage in immature germ cells [20, 24]. Elevated ROS levels in semen producing abnormal spermatozoa are a major cause of low fertility and even infertility. For example, males with high ROS levels in their semen, even without infertility, typically exhibit low fertility potential [23]. Numerous studies have reported that elevated ROS levels are cytotoxic and can lead to problems with sperm motility, count, and viability. Since sperm motility is directly related to mitochondrial function, ultrastructural defects in sperm mitochondria are associated with reduced sperm motility in humans [21]. The presence of abnormal spermatozoa in the semen significantly increases ROS production and leads to mitochondrial dysfunction. Sperm mitochondria constantly supply energy for sperm motility, so any metabolic

disruption in the electron transport chain can significantly increase mitochondrial ROS production, thereby affecting sperm motility. In males experiencing infertility, seminal ROS levels are significantly higher, and antioxidant capacity is reduced compared to fertile controls. ROS formation can affect various enzymes in the seminal fluid, such as superoxide dismutase (SOD), catalase (CAT), or glutathione peroxidase (GPx), which protect spermatozoa from ROS attack. Kesari et al. reported that the reduction in glutathione levels during sperm production, as a result of induced oxidative stress, was associated with a loss of sperm membrane integrity. They also found a reduction in glutathione and superoxide production after exposure to radiation at various frequencies and power levels [23]. Additionally, Vakalopoulos et al. reported that radiotherapy could have both temporary and permanent adverse effects on male fertility. However, there is strong evidence suggesting that radiotherapy is more harmful than chemotherapy in patients with testicular cancer. The doses used in radiotherapy range from 3000 to 7000 cGy, and it has been found that these doses have mutagenic, teratogenic, and embryotoxic effects [21].

In studies investigating the effects of radiotherapy on spermatogenesis, the general consensus is that spermatogonia begin to be affected by doses as low as 0.1 Gy, leading to a reversible reduction in sperm production up to 1.5-2 Gy. Doses between 2-4 Gy cause damage that may be reversible only after many years, while exposure above 5 Gy generally leads to permanent azoospermia and infertility [20-22].

Radiation can also affect spermatogenesis through the endocrine system. Radiation exposure is considered a risk factor for the release of FSH and LH from the pituitary. LH stimulates Leydig cells to produce testosterone, so a reduction in testosterone levels can significantly affect sexual differentiation in the fetus and spermatogenesis in adults. FSH stimulates Sertoli cells in the testes, activating the seminiferous tubules, which in turn facilitates sperm production and the conversion of testosterone into estradiol. Researchers have also reported that radiation is responsible for decreasing melatonin levels in the pineal gland. Oktem et al. found that increased oxidative stress from microwave radiation caused a reduction in melatonin concentrations. Melatonin exerts an anti-gonadotropic effect primarily at the hypothalamus and pituitary levels, reducing testosterone secretion in Leydig cells; as a result, testicular size decreases, and testosterone production is insufficient. Melatonin regulates the pulse of LH secretion at the hypothalamic level, which affects the secretion of gonadotropins FSH and LH. Consequently, this can alter the production of gonadal sex steroids and cause changes in the reproductive cycle [20, 21]. These gonadotoxic effects suggest that the male

who has been exposed to radiation may transmit hereditary effects to future generations. Surprisingly, studies on this issue have yielded contradictory results. Some studies show that children of fathers exposed to radiation are more prone to oncological diseases, while other studies report no such effect or only minimal changes. Further research is needed to reach a more definitive conclusion on this matter [20, 23].

1.2.2.4. Histopathogenesis of Radiation in the Male Reproductive System

The histopathological effects of radiation are typically characterized by DNA damage and apoptosis. The relatively high radiosensitivity of the male reproductive system makes this histopathological process more distinctly observable. Spermatogonia experience a reduction in their numbers and function through DNA damage and apoptosis, leading to a decrease in both the quantity and quality of produced sperm [27]. Seminiferous tubules may shrink and lose their structural integrity. Spaces between cells widen, and the walls of the tubules weaken. This inhibits sperm production and interferes with the proper function of the tubules. Sertoli cells, which provide essential nutrients for spermatogenesis and support regular cell division, are reduced in number by radiation, making the tubules nonfunctional. The interstitial tissue containing Leydig cells outside the seminiferous tubules may also be affected by radiation. Exposure reduces the number and function of these cells, inhibiting testosterone production. This leads to hormonal imbalances that affect sperm production [28]. The walls of the epididymis may become thinner, and damage to this transport duct can interfere with sperm storage and maturation. In a study on rhesus monkeys, the likelihood of sperm presence in the epididymis decreased as exposure increased [29].

1.2.3. Cytoprotective and Radioprotective Agents in Radiotherapy

Amifostine (WR-2721) is the only cytoprotective agent with confirmed reliability in clinical use and is widely employed to mitigate organ damage caused by gamma radiation in radiotherapy applications [30]. Due to its sulfhydryl group, there is strong evidence suggesting that it can exhibit cytoprotective potential in various organs when exposed to radiotherapy or ionizing radiation [31]. Additionally, Amifostine has been found not to demonstrate selective cytoprotective effects on transformed tumor cells while protecting healthy cells [32]. Despite being FDA-approved and recognized as a promising cytoprotective agent with antioxidant potential, Amifostine's reported side effects, such as nausea and hypotension, can sometimes prevent the completion of the co-modality treatment [33]. Therefore, medical and life science researchers are investigating ways to alleviate Amifostine's

toxic potential or exploring alternative approaches. Experimental studies and clinical observations have provided strong evidence that non-essential amino acids such as Glutamine, anti-inflammatory agents like Benzydamine, multifunctional agents like Petoxifilin, immunomodulatory drugs, and phyto-radioprotective agents could replace Amifostine or serve as co-modality treatments [34]. This section will discuss plant-derived agents that are considered promising for cytoprotection and radioprotection, with potential applications in gonadal protection and the preservation of reproductive health.

1.2.3.1. Current Status of Radiotherapy, Reproductive Health, and Phytotherapeutic Agents

Numerous studies have reported the protective effects of both the FDA-approved cytoprotective agent Amifostine and various plant-derived compounds on radiotherapy-induced reproductive damage. In an animal study by Andrieu et al., animals treated with 200 mg/kg Amifostine showed a reduction in radiotherapy-induced histopathological changes at both light microscopic and ultrastructural levels. Furthermore, testicular volume improved significantly in animals treated with Amifostine following a 6 Gy radiation dose [35]. However, the same study also noted a visible reduction and damage in testicular tissue and sperm cell count in animals exposed to radiation without Amifostine treatment, suggesting that pre-treatment with Amifostine could provide protective effects. This literature raises some concerns about the reliability of Amifostine, particularly in relation to the radiation therapy protocols, exposure doses, and duration. In another study that examined DNA fragmentation due to radiotherapy using the TUNEL assay, Amifostine was found to be effective in eliminating pathological changes in the testis and significantly reducing DNA fragmentation [36].

In addition to Amifostine, several other agents and phytochemical compounds have shown cytoprotective potential in radiotherapy applications. An experimental study on animals exposed to 2 Gy abdominopelvic radiation found that supplementation with Vitamin C alleviated testicular pathological changes [37]. This study also reported that the vitamin supplementation regulated epididymal sperm levels and potentially improved fertility. Some plant-derived agents have been identified for their potential to protect the female genital system, ovarian function, and reproductive health in the context of gamma radiation exposure. In an experimental study, Prasada et al. demonstrated promising results of *Alocasia indica* treatment in female mice subjected to 2.9 Gy radiotherapy. This treatment alleviated irregular levels of FSH, LH, estrogen, progesterone hormones, cytokine levels,

and oxidative stress induced by radiotherapy [38]. Observations from this study also showed that phytotherapeutic treatment could mitigate the reduction in follicle numbers and hemorrhaging in ovarian tissue, as well as histopathological changes in uterine tissue induced by radiation. In another study, histopathological examination of ovarian tissue in animals exposed to 3.2 Gy radiation revealed a significant reduction in ovarian follicle reserve, regression of preantral follicles, shrinkage of uterine volume, and a marked increase in inflammatory response [39]. However, animals treated with plant-derived resveratrol showed significant improvements in reproductive parameters.

In conclusion, gamma radiation-based radiotherapy plays a crucial role in cancer treatment and is likely to remain in use until alternative and more reliable radiotherapy methods become widespread. Depending on the radiation dose plans used in cancer treatment, radiotherapy can lead to subfertility or infertility. Although some preventive methods and co-modalities exist, there is a clear need for the discovery of new, potent cytoprotective agents to more effectively harness the power of ionizing radiation in cancer therapy. This medical and scientific approach has the potential to directly impact healthcare costs, survival rates, and the post-treatment quality of life for patients.

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