Chapter

Radiogenomics: A Personalized Strategy for Predicting Radiation-Induced Dermatitis

Beatriz Regina Lima de Aguiar, Eliete Neves Silva Guerra and Paula Elaine Diniz dos Reis

Abstract

Although radiation therapy (RT) planning and execution techniques have evolved to minimize radiotoxicity to a considerable extent, adjacent tissues still receive a substantial dose of ionizing radiation, resulting in radiotoxicities that may limit patients' quality of life. Depending on the location of tissue injury and the severity of the cellular response, there may also be a need to interrupt RT, thus interfering with the prognosis of the disease. There is a hypothesis that genetic factors may be associated with individual radiosensitivity. Recent studies have shown that genetic susceptibility accounts for approximately 80% of the differences in toxicity. The evolution of genomic sequencing techniques has enabled the study of radiogenomics, which is emerging as a fertile field to evaluate the role of genetic biomarkers. Radiogenomics focuses on the analysis of genetic variations and radiation responses, including tumor responses to RT and susceptibility to toxicity in adjacent tissues. Several studies involving polymorphisms have been conducted to assess the ability to predict RT-related acute and chronic skin toxicities, particularly in patients with breast and head and neck cancers. The purpose of this chapter is to discuss how radiogenomics can help in the management of radiotoxicities, particularly radiodermatitis.

Keywords: neoplasms, radiation therapy, radiodermatitis, radiation genomics, single-nucleotide polymorphism

1. Introduction

1.1 Radiation therapy (RT)

Radiation therapy (RT), a local therapeutic modality for cancer, uses beams of ionizing radiation to inhibit or control the growth of tumor cells and can be practiced alone or in conjunction with other therapies [1]. It is used in approximately 50–60% of cancer treatments for curative and palliative purposes [1–3].

There are two modalities of RT, namely brachytherapy and teletherapy. Brachytherapy uses a source of ionizing radiation that is in contact with tumor tissue and allows higher doses of radiation to reach the target tissue [4, 5]. Teletherapy,

also called external RT, is the most common type of RT and is performed using machines, typically linear accelerators, which allow a source of ionizing radiation to be positioned at a certain distance from the patient and programmed to focus on the tumor [4, 5].

1.1.1 Mechanism of action of RT

For a normal cell to be able to multiply, the cell cycle takes approximately 10–20 hours [6]. Tumor cells tend to proliferate faster. During the G2 and mitotic (M) phases of the cell cycle, chromatin is more compact and hinders the action of repair enzymes, thereby increasing the probability of DNA damage [3]. Therefore, these are the two phases of the cell cycle (G2 and M) in which cells are the most radiosensitive [3, 4, 6, 7].

In addition to DNA damage, other mechanisms of cell damage can result from the use of ionizing radiation, which induces cell death. The type of cell death induced by ionizing radiation depends on the cell type, cell cycle stage, DNA damage repair capacity, ionizing radiation dose, and cellular microenvironment [3, 7, 8]. This can occur through direct or indirect mechanisms.

The direct mechanism of cell death induced by RT involves the absorption of energy by the cellular biological environment, and this energy interacts directly with DNA and proteins, causing damage that can occur up to a time after tissue irradiation [4, 6, 8]. In the indirect mechanism, ionizing radiation interacts with molecules that constitute the cell environment, primarily water, increasing the concentration of free radicals that can enhance radiosensitivity and promoting cellular damage [4, 6]. Double-strand DNA breaks can also be induced by reactive oxygen species, which are naturally produced during cellular metabolism [7].

The recognition of DNA damage induced by ionizing radiation promotes the activation of a cascade of signals that, depending on their function, will determine whether the fate of cell repair, cell cycle progression, or apoptosis [9]. Furthermore, increasing the concentration of reactive oxygen species can activate genes that induce tissue inflammation or increase oxidative stress, thereby affecting radiosensitivity [9]. The inflammatory cascade can also be induced by exposure to ionizing radiation [1].

Cellular response to radiation is also regulated by gene activation cascades and signal transduction proteins, which involve the *PI3K/AKT, MAPK/ERK, NF-κB* and *TGFβ* pathways [10]. The *MRE11-RAD50-NBS1* complex and *53BP1*, *γH2AX*, and *MDC1* genes repair DNA end fragments [9]. The *ATR* and *ATM* genes are responsible for activating DNA repair processes by homologous recombination and non-homologous end splicing, respectively, after double-strand breakage [8, 9, 11]. These genes also interact with other genes that are essential checkpoints for verifying the integrity of genetic material in the phases of the cell cycle [9, 11]. If DNA damage is significant, cell death occurs [8]. Any alteration in the function of the genes that participate in the pathways, which regulate cellular responses to radiation, influences DNA repair, cell cycle progression, and cell death by apoptosis.

Considering that tumor cells multiply faster than normal tissue cells, they tend to go through the G2 and M phases of the cell cycle more often. For RT to be effective in controlling the growth and multiplication of tumor cells, the planned total ionizing radiation dose is subdivided into daily doses (dose fractionation). RT fractionation regimens aim to reach the largest number of tumor cells in the most radiosensitive phases of the cell cycle (G2 and M), thereby increasing the therapeutic effect of ionizing radiation. The dose of ionizing radiation absorbed per unit mass in RT is defined

as Gray (Gy) [5]. From the first dose of ionizing radiation, free radicals, reactive oxygen species, double-strand DNA breakage, and recruitment of the inflammation cascade are generated [1]. Total dose fractionation also aims to minimize adverse effects on healthy tissues adjacent to the tumor [5].

1.1.2 Adverse effects of RT

Toxicity resulting from exposure to ionizing radiation is very common [1, 2]. Considering that some healthy tissues, including the skin and mucous membranes, have a high proliferation capacity, fractioned doses also reach these tissues, promoting adverse reactions [1].

Adverse effects of RT are characterized by reactions that occur in tissues adjacent to the tumor or in contact with ionizing radiation during dose administration. These adverse effects can be acute or chronic, depending on the time of onset [7].

Acute adverse effects appear during RT or up to 3 months after completion in tissues with a high proliferation capacity [3, 4, 7]. For example, tissues such as the skin and mucous membranes are frequently affected [3, 4, 7]. The chronic effects appear from 3 months after the end of RT to years later, affecting tissues composed of cells with lower proliferation capacity such as cardiac, muscular, and subcutaneous tissue [3, 4, 7, 12].

Depending on the severity of the acute reactions, treatment may need to be interrupted [7]. These reactions cause pain and discomfort and may negatively impact patients' quality of life [3].

1.2 Acute radiation dermatitis (ARD)

Acute radiation dermatitis (ARD) is a skin reaction with a high incidence that affects cancer patients undergoing RT for up to 3 months after the end of the treatment [13, 14]. Approximately 95–100% of cancer patients have some degree of ARD during RT, which is very common in patients treated for breast and head and neck cancer [15–17]. The first effects of ionizing radiation on the skin are expected to appear 2–4 weeks after the first dose of RT [15].

ARD usually starts with hyperpigmentation of the irradiated area, followed by mild or transient erythema, intense erythema, dry desquamation, and moist desquamation, and in more severe cases, leads to hemorrhage, necrosis, and ulceration (**Figure 1**) [15]. Generally, RT is interrupted when patients present with disseminated moist desquamation and the skin tissue does not progress to more severe reactions.

1.2.1 Pathophysiology

The pathophysiological mechanism underlying ARD development is similar to that of the mechanism of ionizing radiation on the tumor, i.e. through direct and indirect DNA damage mechanisms. The effects of RT on skin tissue are cumulative and add up to each fraction of the ionizing radiation received [15, 18].

Tissue injury occurs through alterations in the double-stranded DNA of epithelial cells or through an increase in the concentration of reactive oxygen species in the intracellular environment [15, 16]. These lesions primarily affect the basal cells of the epidermis, which cannot self-renew in sufficient time to reconstitute the tissue [15]. Furthermore, ionizing radiation promotes the activation of the inflammatory cascade in the skin tissue [15, 16, 18].

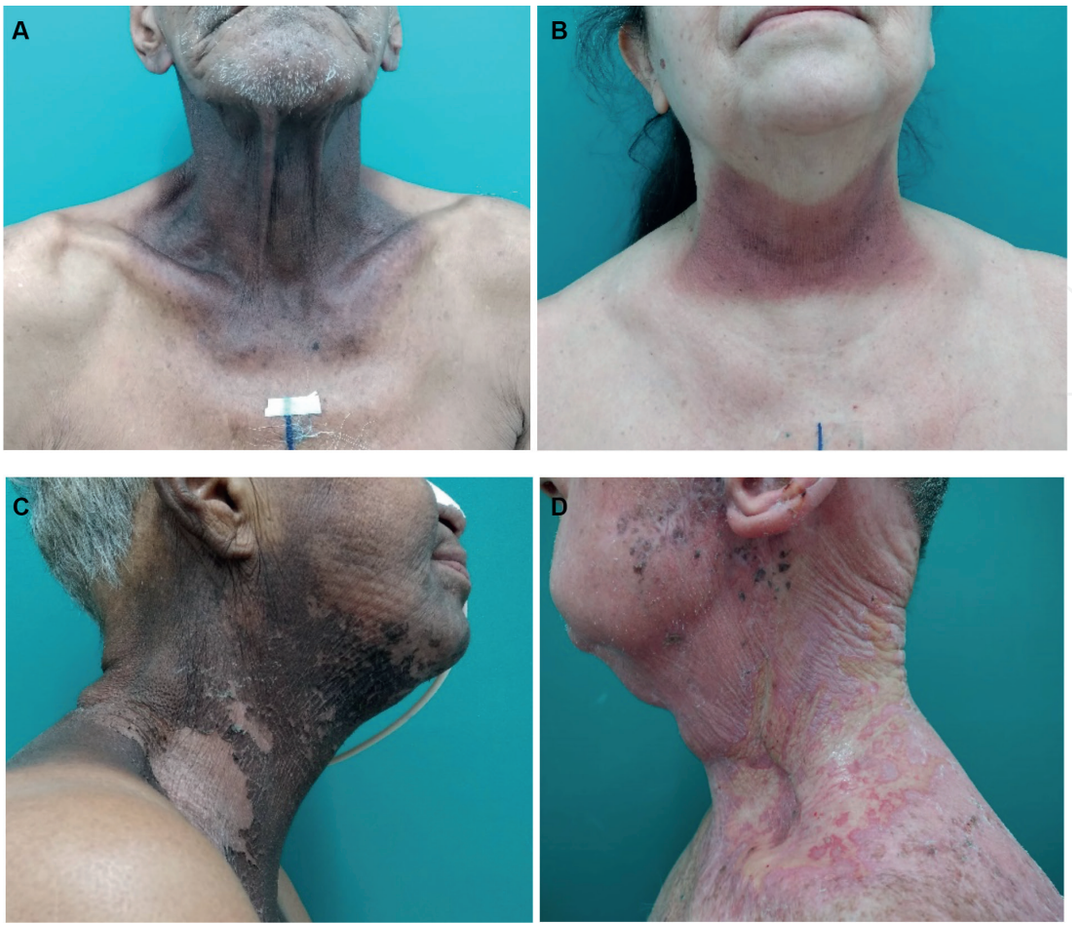

Figure 1.
Signs of ARD in head and neck cancer patients: A) hyperpigmentation; B) erythema; C) dry desquamation; D) moist desquamation. Source: Digital collection of the interdisciplinary Laboratory for Applied Research to clinical practice in oncology (LIONCO).

Skin hyperpigmentation occurs due to excessive stimulation of melanin production triggered by exposure to ionizing radiation [14, 15].

Local erythema starts soon after the first fraction dose of RT and is more intense around the second week due to vasodilation and increased vascular permeability [13–15]. This then initiates an inflammatory reaction with the release of chemokines and cytokines (primarily interleukins and TNF-α), which control endothelial cell adhesion and recruit immune cells [15]. This process can be observed as the manifestation of intense erythema [15].

Dry desquamation usually appears at an accumulated dose of approximately 30 Gy [14], between the third and fourth week [13]. This occurs as a result of a rapid compensatory attempt to renew epidermal basal cells, which occurs faster than the elimination of damaged epidermal cells [15]. In addition, RT promotes lesions in the cells of the sebaceous glands and hair follicles, which causes increased dryness of the skin and loss of hair in the treated area [15]. When the entire basal layer is destroyed, moist desquamation occurs after approximately 4–5 weeks of treatment [13] with barrier disruption and exudate production [15].

It is important to emphasize that these cellular reactions will be observed in the skin corresponding to the irradiated area and do not necessarily need to occur gradually. In addition, the time to the onset of each degree of reaction may vary among patients. Scales are generally used to measure and monitor the evolution of

ARD during treatment. The Common Toxicity Criteria for Adverse Events (CTCAE) scale [19] and the Radiation Therapy Oncology Group (RTOG) scale [20] are widely used.

1.2.2 Clinical management

Several regular skin care guidelines, including cleaning the irradiated area daily using neutral soap and warm water without friction on the skin, drying gently, keeping the treatment area protected from sun exposure, and wearing looser clothes to avoid friction [13, 14, 16], are well documented in literature and patients should be oriented to these before beginning RT.

Although there are several skin care recommendations for the treated area before and during RT, these measures do not definitively prevent the development of ARD. However, it is still no consensus in the literature on the products that are effective in preventing ARD [7, 21, 22]. Therefore, the use of predictive mechanisms for the development of ARD would be a useful tool for improving treatment planning.

1.2.3 Risk factors and individual Radiosensitivity

The following risk factors predispose patients undergoing RT to develop severe ARD:

- Treatment-related factors, including volume of treated area, tumor location (superficial or deep), total dose of ionizing radiation, fractional dose, duration of treatment, use of boost, and combination with other cancer treatment modalities [13, 15, 23].

- Patient-related factors, including exposure to solar radiation (UVA and UVB), skinfolds, humidity in the irradiated region, smoking, alcohol consumption, nutritional status, body mass index (BMI), sensitivity of the exposed skin, preexisting skin diseases, and genetic factors [13, 15, 23].

Risk factors for ARD can be considered determining factors for individual radiosensitivity. Radiosensitivity refers to the susceptibility to adverse effects resulting from exposure to ionizing radiation.

One of the challenges associated with planning the treatment of cancer patients is the identification of factors that influence the increase in individual radiosensitivity and decrease in tissue repair capacity [2, 3, 24]. However, patients with similar risk factors and treatment regimens may have different degrees of ARD. Furthermore, literature suggests that genetic factors can influence the tissue response to ionizing radiation [2].

1.3 Genetic markers and radiotoxicity

Research on factors that influence the development of adverse reactions to RT has investigated the contribution of genetic factors to these reactions [25]. This concept emerged from the identification of syndromes that make individuals more sensitive to ionizing radiation, such as the ataxia-telangiectasia syndrome resulting from mutations in genes that respond to DNA damage and repair [26, 27]. Thus, biomarkers may help in treatment planning.

Thus, radiogenomics has emerged as an area of study that aims to identify biomarkers that can predict adverse reactions in cancer patients undergoing RT or to identify individuals who are more susceptible to developing a severe degree of these reactions [3, 10, 28].

Biomarkers are molecules/biomolecules that can be measured in biopsy samples, body fluids, and feces to indicate the state of normal metabolic processes, diseases, and responses to a particular treatment [3, 29].

In 2009, the Radiogenomics Consortium (Manchester, United Kingdom) was established and supported by the National Cancer Institute (NCI) [30]. In 2019, 133 institutions from 33 countries participated in the Consortium [31]. The objective of the Radiogenomics Consortium was to establish collaborations between countries so that studies on the association between biomarkers and adverse reactions to RT could be carried out in large cohorts [10, 32] in order to identify molecular pathways that participate in the development of adverse reactions to RT and variants in the genome that are capable of predicting the development and severity of these reactions [10, 30, 31, 33].

The primary biomarkers studied by the Radiogenomics Consortium are single-nucleotide polymorphisms (SNPs) [31, 34]. SNPs are considered suitable genetic markers in studies on their association with phenotypic characteristics, as they are frequent in populations and are easily genotyped [35]. Furthermore, samples for single-nucleotide polymorphism (SNP) screening can be obtained from any normal tissue, considering that polymorphisms are present in all normal cells, including blood cells [33].

1.3.1 Single-nucleotide polymorphism

The DNA sequences of any two individuals in the world are approximately 99.9% similar to each other [36, 37]. Variations in only 0.1% of the genome make individuals phenotypically different from each other [3, 37–39]. Among these 0.1% variations, approximately 99% are due to SNPs [40].

Mutations and SNPs are genetic variants present at specific positions in the DNA sequence. SNPs are considerably common among individuals and have a probability of 1% or more of being identified in an individual, whereas "gene mutation" refers to variations in the DNA that are present in less than 1% of the population [36, 37]. Although these definitions are well established, the nomenclature remains confusing [36]. Condit et al. [41] suggest the use of the terms "genetic variant" or "genetic alteration" to replace the definitions of mutations and polymorphisms that can be complemented with the terms "pathogenic" or "benign" [36, 42]. However, the establishment of a generalist nomenclature has still been discussed.

SNPs are genetic variants that occur with the replacement of a single nucleotide in a genome sequence [27]. The variation that results in SNP can occur in non-coding regions such as intergenic and intron regions, which will not promote phenotypic changes, and in the exon coding region, which may or may not modify the gene function and consequently the phenotype (**Figure 2**) [35, 37, 44]. Although exchange of a nucleotide at a specific position can be performed by any other nucleotide (C, G, A, or T), SNPs are generally biallelic [35, 45].

To understand mechanism by which SNPs occur in DNA and their impact on the phenotype, let us look at the following example:

On chromosome 19, the locus that encodes *TGFβ* is most commonly found in exon 1, at a guanine nucleotide (G) at position 869. On the complementary strand of DNA, G pairs with a cytosine (C) encoding the amino acid Proline (Pro) at codon 10

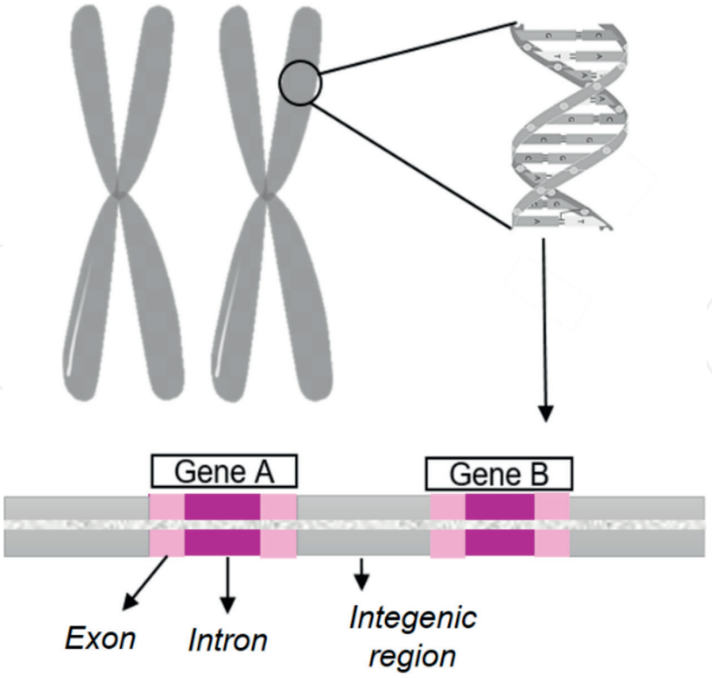

Figure 2.
Schematic representation of the non-coding (intron) and coding (exon) region of a gene. Generated with reference to the schematic representation by Alberts et al. [43].

(**Figure 3A**). Considering that it is most frequently found in the population, C, in this example, is called the wild allele. However, in some individuals, an exchange of G for adenine (A) at this position has been observed (**Figure 3B**). This exchange also leads to a change in the complementary strand of DNA, that is, the exchange of C for thymine (T), thus encoding the amino acid leucine (Leu) (**Figure 3C**). In this example, the T allele is called a variant allele because it is less frequent in the population. Considering that this allelic variation (G > A) is present in more than 1% of the population, it is called an SNP. This *TGFβ* SNP is referred to as Pro10Leu or encoded as rs1800470.

The human genome is diploid; that is, we inherited 23 chromosomes from the father and 23 from the mother, which are organized into pairs by similarity to each other. This organization into pairs of similar chromosomes is called homologous chromosomes, which have very similar nucleotide sequences. Therefore, SNPs can occur on one chromosome or on a homologous pair of chromosomes, and hence, they can be classified as homozygous for the wild allele, homozygous for the variant allele, or heterozygous (**Figure 4**).

1.3.2 Techniques for studying single-nucleotide polymorphisms

The candidate gene approach has been used to assess the association between SNPs and adverse reactions to RT. For this, genes that are already known to participate in the molecular mechanism underlying the development of adverse reactions are selected [39, 46]. Seibold et al. [47] performed a study of candidate genes involved in oxidative stress to verify their ability to predict late toxicity in 753 breast cancer patients who underwent RT. The study showed that breast cancer patients carrying the rare allele for the SNP rs2682585 in *XRCC1* had a low occurrence of late cutaneous toxicities (OR: 0.77; 95% CI: 0.61–0.96; p = 0, 02) [47]. The association of this SNP with late skin toxicity in breast cancer patients undergoing RT has been validated by

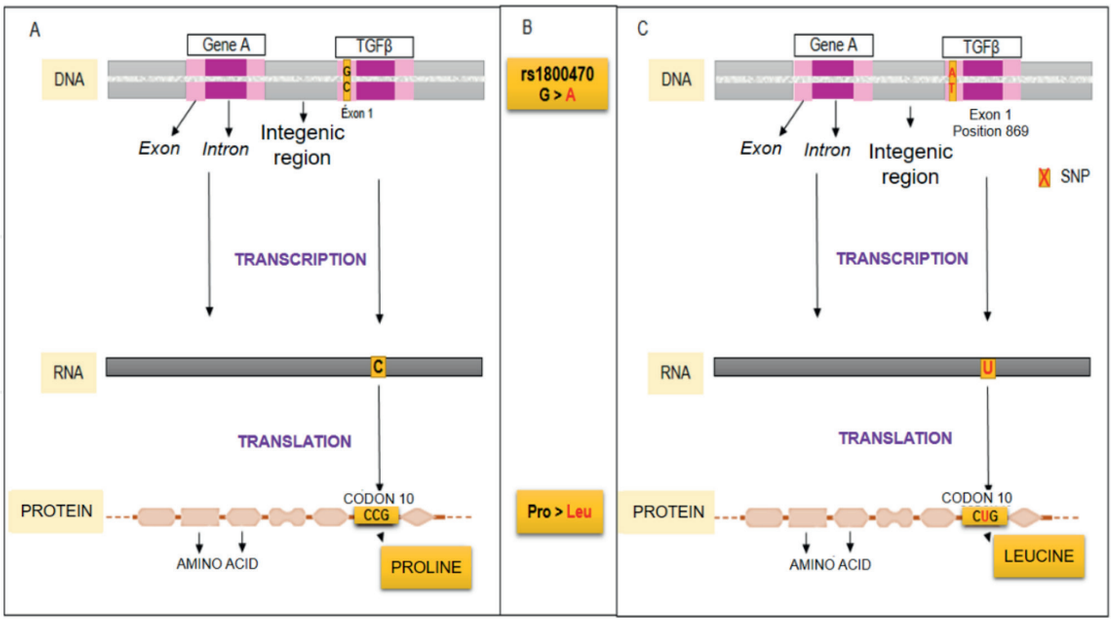

Figure 3.
Schematic representation of the rs1800470 SNP in TGFβ. A) the nucleotide sequence that makes up TGFβ will be transcribed into RNA and one of the strands will be translated into a protein that has proline (pro) at codon 10; B) rs code of the SNP in TGFβ (rs1800470) and the respective exchange of base (G > a) and protein (pro>Leu); C) SNP occurs at position 869, of exons 1, of TGFβ (G > a) and originates a complementary strand with a thymine at this position. Thymine will be transcription into uracil which will give rise by translation to a protein with leucine (Leu) at codon 10.

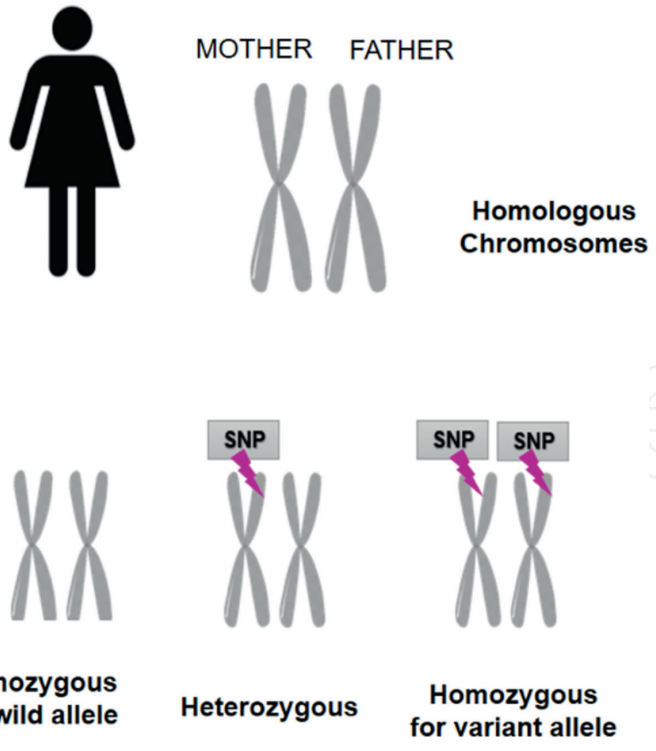

Figure 4.
Classification according to the occurrence of SNP in homologous chromosomes.

members of the Radiogenomics Consortium [28]. An important challenge in developing such research is that researchers must have basic knowledge about molecular biology and the effects of ionizing radiation on DNA [27].

Other techniques that investigate susceptibility genes, including genome-wide linkage studies (GWLS) and genome-wide association studies (GWAS), are used to conduct a broader investigation of all genes rather than an investigation of those genes already known to participate in molecular pathways involved in disease development [37]. These techniques are based on full-genome scanning and are extremely useful for investigating polymorphisms that may be associated with adverse reactions to RT [39, 46]. However, they are rarely used in studies on the association between polymorphisms and ARD. The Radiogenomics Consortium aims to obtain resources to enable the evaluations in large cohorts using the GWAS technique [30, 32].

2. The association of SNPs with acute radiation dermatitis prediction

Studies have investigated the association between SNPs and the severity of ARD that developed at the end of RT, primarily in patients receiving RT for head and neck and breast cancer.

2.1 Breast CANCER patients

A systematic review [48] of 16 cohort studies at low risk of bias, with a total of 4742 breast cancer patients treated with radiotherapy, summarized the data on whether SNPs predict ARD. Before the start of radiotherapy, all studies collected blood samples to identify SNPs and considered any manifestation of moist desquamation as a severe degree of ARD. Several studies included in this review presented statistically significant associations between SNPs and ARD. Twenty-nine SNPs were significantly associated with increased susceptibility to developing severe ARD and fifteen SNPs were significantly associated with decreased susceptibility to severe ARD ($p < 0,05$) However, it was not possible to compare the results in different samples because these associations were found in only one individual study. Furthermore, a wide variety of SNPs are being evaluated in individual studies, which makes it difficult to synthesize the data in a meta-analysis.

Considering the individual studies included in this systematic review, two SNPs had a significant association in more than one study, but with controversial results.

The rs8193 SNP in *CD44*, with CT and CT + TT genotypes, was associated with a 2.68-fold and 2.31-fold increase, respectively, in the risk of developing severe ARD in one study [49]. However, another study [50] found that the recessive model (TT) individually decreased the risk of developing severe ARD by 52%. *CD44* is a gene that involves transmembrane cell adhesion that is highly expressed on the surface of the dermis; however, its mechanism of action in healing remains unclear [51–56]. The meta-analysis found that the CC genotype is associated with the development of mild ARD, which did not manifest moist desquamation, and the CT genotype is associated with the development of severe ARD. However, with considerably low evidence certainty, further studies are required to investigate this SNP.

The rs3744355 SNP in *LIG3* was associated with the occurrence of ARD in one study ($p = 0.0046$) [57], but the authors did not report further information. Another study [50] found that the dominant pattern of this SNP was associated with a 68% decrease in the risk of developing severe ARD. *LIG3* acts on the DNA repair pathway by base excision, resulting from exposure to reactive oxygen species produced by exposure to RT [12, 57, 58].

Despite being evaluated in eight studies that composed this systematic review, the SNP *XRCC1* (rs25487) demonstrated a prevalence of 31% in breast cancer patients;

however, the data were not sufficient to allow the assessment of the association of this SNP with the severity of ARD.

The most prevalent SNPs were rs1800469 in *TGFβ1* (41%) and rs3957356 in *GSTA1* (36%). *TGFβ1* encodes a protein that acts on the inflammatory response pathways by repairing DNA lesions; however, it is not yet known whether SNPs can affect the function of this protein [59, 60]. *GSTA1* is involved in the production of reactive oxygen species, and SNPs can promote increased radiosensitivity through indirect damage to the DNA of skin cells [61]. Meta-analysis of genome association studies found that the CT genotype of the SNP rs3957356 in *GSTA1* increases the risk of severe ARD by approximately 6-fold, with low certainty of evidence.

Other SNPS associated with the development of mild and severe ARD in this systematic review are reported in **Table 1**.

Considering that these SNPs have presented low or considerably low certainty of evidence of association with ARD, further studies should be carried out to evaluate these SNPs to verify the existence of this association.

2.2 Association IN patients with head and neck CANCER

There is still no systematic review that summarizes the data on SNPs in the prediction of ARD in patients with head and neck cancer. Therefore, the evidence discussed here comes from a quick literature search.

The rs3755557 SNP in *GSK3β* in the allelic model was reported [62] to have a statistically significant association with the development of severe ARD, considered to be a manifestation of moist desquamation. This gene participates in a number of tissue repair and inflammation pathways [63]. Therefore, it is hypothesized that polymorphisms in this gene may be associated with loss of function in the pathways and decreased tissue repair [56].

Borchiellini et al. [64] demonstrated an association between the GG genotype of SNP rs2279744 in *MDM2* and a 1.23-fold increase in the risk of severe ARD. This gene is responsible for *TP53* degradation [65].

SNPs associated with severe ARD			**SNPs associated with mild ARD**		
Gene	**SNP**	**Genotype**	**Gene**	**SNP**	**Genotype**
Wild homozygote			**Wild homozygote**		
PTTG1	rs3811999	CC	*PTTG1*	rs2961952	GG
PTTG1	rs2961950	AA	*CD44*	rs8193	CC
MAD2L2	rs2294638	GG			
MAT1A	rs2282367	GG			
Heterozygous			**Heterozygous**		
GSTA1	rs3957356	CT	*PTTG1*	rs3811999	GG
CD44	rs8193	CT	*MAT1A*	rs2282367	CC
SH3GL1	rs243336	GC			
			Variant homozygote		
			OGG1	rs2075747	AA

Table 1.
Single-nucleotide polymorphisms (SNPs) associated with acute radiation dermatitis (ARD) in the study by Aguiar et al. [48].

XRCC1 plays an important role in DNA repair following base excision damage [66]. Nanda et al. [67] and Raturi et al. [68] found that polymorphic variants in *XRCC1* for the SNP encoded by rs1799782 increased the risk of developing severe ARD. Additionally, Li et al. [69] found that polymorphic variants in this gene for the SNP encoded by rs25487 also increased the risk of developing severe ARD.

3. Conclusion

Severe degrees of ARD may cause local pain and burning, in addition to having a major impact on patients' quality of life and body image. Methods capable of predicting the occurrence and severity of ARD could improve RT planning. In addition to clinical tumor data and baseline data on patient characteristics, such as exposure to risk factors for ARD, the assessment of SNPs that can predict ARD could assist in patient follow-up and allow personalized RT planning. The use of predictive radiotoxicity genetic assays will allow patients who are more resistant to RT to receive higher doses of treatment without causing serious damage to adjacent tissues. Additionally, patients with lower RT tolerability receive another type of treatment or a lower dose of RT.

Thus, early detection of ARD susceptibility can improve the quality of life of patients who may develop severe ARD and the costs associated with the management of this radiotoxicity in the health care system.

Despite the promising role of SNPs in predicting ARD, studies have yielded inconsistent results and are not sufficient to confirm a significant association. Further studies are needed to confirm this hypothesis. We suggest that genes that have already been reported to have a statistically significant association in at least one study should be investigated in future.

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Author details

Beatriz Regina Lima de Aguiar, Eliete Neves Silva Guerra
and Paula Elaine Diniz dos Reis*
University of Brasília, Brasília, Brazil

*Address all correspondence to: pauladiniz@unb.br

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